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VOLUME 8  
1929

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.





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## A FATAL CASE OF STRONGYLOIDOSIS IN MAN, WITH AUTOPSY

THE LIFE CYCLE OF *STRONGYLOIDES INTESTINALIS* IN MAN \*

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SAN FRANCISCO

The following report of an acutely fatal case of infestation with *Strongyloides intestinalis* is of interest because the observations seem to throw new light on some obscure problems connected with the disease.

### REPORT OF CASE

O. H., an American railroad engineer, aged 36, was born in Texas and lived there all his life until he came to California six months before entering the hospital. On Nov. 25, 1928, he contracted a cold in the chest. Shortly thereafter he began to have a sore mouth and by December 20, had developed a sore throat and hoarseness. On December 29, he began to vomit everything taken by mouth. At the same time he had diarrhea and bled from the anus. He had had a similar attack lasting seven days two years before, while still in Texas.

When he entered the hospital on Dec. 31, 1928, he had a marked stomatitis. The inside of his mouth was covered with white plaques of a pasty exudate, which were easily removed from the underlying red mucosa. The entire buccal cavity was involved. The deposits were most marked along the sides of the mouth, under the tongue and in the tonsillar region, including the pillars of the fauces. Bacteriologic examination showed the presence of streptococci. Spirochetes or fusiform bacilli were not found in the smears. It is doubtful whether the stomatitis had any direct connection with the strongyloidosis.

Nothing abnormal was discovered in the patient's chest and abdomen. The anus was surrounded by an area of excoriation, measuring approximately 2 cm. in diameter. On digital examination, the rectum was found to be tender.

The patient's blood pressure was 130 systolic and 85 diastolic. His blood was practically normal, showing 3 per cent eosinophils on the first examination and later 1 per cent.

He vomited considerable quantities of bile-stained mucus and also had marked diarrhea. His stools were examined twice, on January 6 and 10. They contained no gross admixture of blood or pus, but gave a positive reaction for occult blood. No ova or parasites were discovered, although they were looked for.

The patient vomited so much that he became dehydrated. He remained hoarse and appeared rather dull mentally. His stomatitis gradually subsided.

On Jan. 7, 1929, he complained of itching on the hands, chest and legs.

\* Submitted for publication, March 26, 1929.

\* From the Department of Pathology of the Stanford University Medical School.

On the whole, his condition seemed gradually to improve. He vomited less and was beginning to take a moderate amount of nourishment. His diarrhea had stopped to a certain extent. On January 25, however, he felt weak and complained of impaired vision. He became drowsy and spoke incoherently. On January 27, his condition suddenly became alarming, and he died during the afternoon.

A complete autopsy, including an examination of the brain, was done within a few hours of death. The stomatitis had practically disappeared. The only important lesion in the viscera of the chest was an old chronic myocarditis of the anterior wall of the left ventricle with slight dilatation of the left side of the heart. This had caused a chronic passive congestion of the lungs with the development of many heart failure cells. The small bronchi were filled with thick mucopurulent material, and the pulmonary tissue was excessively inflated with air, probably on account of a partial obstruction of the bronchioles by the sticky exudate in them.

The mucous membrane of the stomach was much congested and covered with a solid layer of gray mucus. The lower mesenteric lymph nodes were moderately swollen and gray on the cut surface. The duodenum and jejunum were much congested. The mucosa of the ileum was dark red and slightly dull on the surface. The large intestine was distended with dark-greenish, soft stools, and its mucosa also showed a diffuse congestion, which was particularly well marked in the lower part of the colon and rectum, where the normal gloss on the surface was partly absent.

The rest of the abdominal viscera were normal, except for the accidental presence of several large false diverticula in the upper part of the jejunum.

The case had been puzzling to the clinicians and was not satisfactorily explained by the gross observations at the autopsy, which, as already indicated, revealed merely the presence of a well marked gastro-enteritis of moderate severity and a healed chronic myocarditis with chronic passive congestion of the lungs, which, however, had not been accompanied by any evident disturbance in the systemic circulation. The infection of the bronchi that was also present was hardly of sufficient severity to explain the death of the patient.

The infestation with *Strongyloides* was not discovered until a microscopic examination was made of the gastro-intestinal tract. Fortunately, on account of the early performance of the autopsy, the tissues were well preserved and showed the finer histologic details clearly.

The mucous membrane of the pyloric region of the stomach was filled with mother worms, ova and rhabditiform embryos. Unfortunately, no pieces for microscopic study had been taken from the duodenum and jejunum. No parasites were discovered in the lower part of the ileum, while the mucosa of the colon contained a considerable number of filariform larvae. A few of them were present in the submucosa and in the muscular coat. The larvae were also found in the swollen lower mesenteric lymph nodes. None were encountered in sections of the lungs and of the liver in spite of careful search of several specimens with microscopes equipped with the mechanical stage.

The presence of the parasites had produced relatively little reaction in the gastric mucosa, which showed a slight irregular infiltration with lymphocytes and eosinophilic leukocytes. The mucous membrane of the ileum, although not containing any parasites, was much congested and filled diffusely with eosinophils. Similar histologic changes were present in the large intestines, in which the eosinophilic infiltration was especially well marked in the immediate vicinity of the filariform larvae, so much so that the accumulations of eosinophils about them materially facilitated their discovery in the sections. The surface epithelium

was almost entirely missing in all sections of the gastro-intestinal tract, but this might have been a postmortem change. The inflamed mucosa was not covered with false membranes, nor was there any evidence of ulceration, even microscopically. The mesenteric lymph nodes showed congestion and a diffuse infiltration with eosinophils. This was especially well marked in the vicinity of the larvae which were contained in them.

## COMMENT

In strongyloidosis, the parthenogenic or more probably hermaphroditic (Sandground<sup>1</sup>) mother worms of *Anguillula* or *Strongyloides intestinalis* live in the pyloric part of the stomach, the duodenum and the upper part of the jejunum. As Golgi and Monti<sup>2</sup> first showed, they enter the crypts in order to deposit their ova. This they often do in such a way that their tail ends are folded back and their genital pores exposed at or near the bottom of the invaded crypts. In their progress down the crypts, the worms may pierce the epithelial lining and lie in longitudinal channels within the epithelial cells, or they may compress the epithelium leaving only a narrow border, or they may rub it off entirely from the membrana propria. Askanazy<sup>3</sup> and other investigators were of the opinion that they frequently enter the stroma of the mucous membrane. In my case, careful examination of serial sections did not seem to support this idea. Even when in certain specimens it appeared evident that the worms were outside the crypts, the following sections showed plainly that this was not so and that they were in preformed cavities continuous with the crypts. It is possible, however, that sometimes the mother worms push their way through the thin partition between neighboring glands, coming to lie partly in one and partly in the other, although even this is not certain. I failed entirely to find the open channels that have been described by other authors as being produced by the migrations of the mother worms in the mucosa.

The ova are deposited within the epithelial lining, and the epithelial cells often surround the ova on all sides. Frequently, the ova are behind the epithelium, between it and the membrana propria. The number of ova in each infested crypt varies from one to five. It is evident that the worms can pass from crypt to crypt, probably by withdrawing from one crypt and entering a new one from the lumen, because frequently a series of crypts were seen that contained ova and no mother worms. The ova show all stages of development to the hatching of the rhabditi-form embryos. When the latter leave their egg shells, eosinophilic

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1. Sandground: Biological Studies on Life-Cycle in Genus *Strongyloides* Grassi, 1879, Am. J. Hyg. **6**:337, 1926.

2. Golgi and Monti: Sulla storia naturale e sul significato clinico-patologica delle cosi-dette anguillule stercorali e intestinali, Arch. per le sc. med. **10**:93, 1886.

3. Askanazy: Ueber Art und Zweck der Invasion der *Anguillula intestinalis* in die Darmwand, Centralbl. f. Bakteriologie. **27**:569, 1900.



leukocytes are attracted into the crypts. The embryos leave the crypts and enter the intestinal canal. On their way out of the crypts, they pass through the epithelium or through the lumen of the crypts. In a careful study of microscopic sections, I was unable to convince myself that they ever enter the stroma of the mucous membrane.

The embryos travel down the intestinal canal with its contents. In the feces, they change directly into filariform larvae or develop into sexually mature worms, which copulate and produce fertilized ova. The latter develop into rhabditiform embryos, which, in their turn, change into filariform larvae.

The filariform larvae are different from the rhabditiform embryos and, although more difficult to find, can be easily recognized as such in sections. They are more slender and stain less deeply. Darling<sup>4</sup> called attention to the fact that in fresh specimens they have an active boring motion, while the embryos have a slower wriggling motion. The direct transformation of embryos into larvae can take place within the colon, but the sexual development occurs only outside of the body. For unknown reasons, the relative frequency of the sexual and asexual cycles varies much in different cases and probably at different times in the same case, sometimes to the exclusion of one or the other.

Following Loos' discovery of the penetration of the skin by the larvae of *uncinaria*, van Durme<sup>5</sup> showed that the larvae of *Strongyloides* from a chimpanzee entered the skin of guinea-pigs. This observation has since been confirmed in other animals by Kosuge<sup>6</sup> and in man by Fülleborn.<sup>7</sup> The infection can therefore take place either through the skin or by way of the alimentary tract. The larvae that enter the skin are carried by the blood to the lungs and from there they reach the stomach by way of the bronchi, larynx and esophagus. When the larvae arrive in the stomach, duodenum and jejunum, they develop into the relatively large mother worms, which deposit their ova in the manner already indicated.

Fülleborn<sup>7</sup> made the interesting observation that the entrance of larvae into the skin of uninfected persons does not produce any reaction, while in infected persons it causes a marked local inflammation. He believed that carriers of *Strongyloides* are often reinfected through the

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4. Darling: *Strongyloides* Infections in Man and Animals in the Isthmian Canal Zone, J. Exper. Med. **14**:1, 1911.

5. Van Durme: Quelques notes sur les embryons de "*Strongyloides intestinalis*" et leur pénétration par la peau, Thompson Yates Lab. Rep. **4**:471, 1902.

6. Kosuge: Histologische Untersuchungen über das Eindringen von *Strongyloides stercoralis* in die Haut von Versuchstieren, Arch. f. Schiffs- u. Tropen-Hyg. **28**:15, 1924.

7. Fülleborn: Hautquaddeln und Autoinfektion bei *Strongyloidesträgern*, Arch. f. Schiffs- u. Tropen-Hyg. **30**:721, 1926.

skin near the anus by larvae which have developed in fecal remnants in this region. He could not demonstrate any other possibility of reinfection and came to the conclusion that the host apparently produces antibodies which stop the development of the larvae.

Imperfect histologic studies of the disease in man were made by Normand<sup>8</sup> in 1876. It was he who discovered the parasites in the stools of soldiers returning to France suffering from Cochinchina diarrhea. On the basis of his investigations, he suspected that the worms enter the crypts of the intestine. In 1886, the problem of their relation to the mucosa was attacked with modern methods by Golgi and Monti,<sup>2</sup> who were followed by Riva<sup>9</sup> in 1892, Askanazy<sup>3</sup> in 1900, Strong,<sup>10</sup> Thayer<sup>11</sup> and von Kurlow<sup>12</sup> in 1902, Brown<sup>13</sup> in 1903, Darling<sup>4</sup> and Gage<sup>14</sup> in 1911, and Oudendal<sup>15</sup> in 1926. A fatal infection with *Strongyloides* in a chimpanzee was described in 1922 by Blacklock and Adler.<sup>16</sup> It is of special interest on account of a tumor-like hyperplasia of the mucous membrane in part of the infected region, and also on account of the fact that the chimpanzee died of an acute general infection with the larvae, which were found in the lungs, in which they had produced multiple hemorrhages, and in the bronchi, the pericardium, the spleen and the blood of the right ventricle. Blacklock and Adler<sup>16</sup> surmised that a sufficient number of larvae to cause the fatal infection by way of the skin must have lodged in the crevices of the wooden cage of the animal. In 1923, the intestinal lesions in *Macacus* were studied by Hung-See-Lü and Höppli.<sup>17</sup>

8. Normand: Sur la maladie dite diarrhée de Cochinchine, Compt. rend. Acad. d. sc. **83**:316, 1876.

9. Riva: Sopra un caso di anguillulosi intestinale sperimentale, Arch. di biol. **46**:40, 1892.

10. Strong: Cases of Infection with *Strongyloides Intestinalis*, Johns Hopkins Hosp. Rep. **10**:91, 1902.

11. Thayer: On the Occurrence of *Strongyloides Intestinalis* in the United States, J. Exper. Med. **6**:75, 1901-1905. Strong and Thayer reported the same case. Thayer gave an excellent historical review of the subject to 1902.

12. Von Kurlow: Anguillula intestinalis als Ursache akuter, blutiger Durchfälle beim Menschen, Centralbl. f. Bakteriologie. **31**:614, 1902.

13. Brown, P. K.: The Report of Three Cases in Which Embryos of the *Strongyloides Intestinales* Were Found in the Stool: Autopsy of One Case, Boston M. & S. J. **148**:583, 1903.

14. Gage: A Case of *Strongyloides Intestinalis* with Larvae in the Sputum, Arch. Int. Med. **7**:561 (April) 1911.

15. Oudendal: Die Darmwand bei Anguilliasis intestinalis, Arch. f. Schiffs- u. Tropen-Hyg. **30**:510, 1926.

16. Blacklock and Adler: The Pathological Effects Produced by *Strongyloides* in a Chimpanzee, Ann. Trop. Med. **16**:283, 1922.

17. Hung-See-Lü and Höppli: Morphologische und histologische Beiträge zur *Strongyloides*infektion der Tiere, Arch. f. Schiffs- u. Tropen-Hyg. **27**:118, 1923.

The descriptions of the different investigators in regard to the entrance of the mother worms into the crypts, the deposition of the ova and the development of the embryos agree in a general way. Most authors were of the opinion that both the mother worms and the embryos can enter the stroma of the mucous membrane, and Oudendal<sup>15</sup> insisted that this is the usual path for the return of the embryos to the lumen of the intestine. It is generally agreed that neither mother worms nor embryos can penetrate beyond the muscularis mucosae. As stated, in my case I was unable to find certain evidence that the worms or the embryos ever leave the crypts, although they were often shown penetrating the epithelium and causing a partial destruction of the epithelial lining.

The infestation is usually limited to the pyloric end of the stomach, the duodenum and the upper part of the jejunum, although Riva<sup>9</sup> found mother worms and embryos in the mucosa as far down as the cecum, but none below this point. Von Kurlow<sup>12</sup> reported the presence of a few small worms in the mucous membrane of the colon. It is uncertain whether these were embryos or larvae. Darling<sup>4</sup> made the positive statement that the *strongyloides* do not invade the mucosa of the large bowel and that for this reason they cannot be incriminated as a causative agent in diarrhea.

What in the end becomes of the mother worms is not known. Probably they die and disintegrate in the intestinal contents; at any rate, dead mother worms have never been discovered in the intestinal wall and have only rarely been found in the stools.

The filariform larvae have not been identified in the intestinal wall except in the remarkable fatal case reported by Gage,<sup>14</sup> in which during life larvae were present in the sputum. In microscopic sections in this case, they were seen deep in the lymph spaces of the wall of the duodenum and jejunum and in the alveoli of the lungs. The transformation of the embryos into the filariform larvae must have taken place immediately in the upper intestine. An invasion of the wall of the colon is not mentioned. From the description, it is not clear whether the colon was examined microscopically. A similar penetration of the intestinal wall by the larvae probably also had occurred in Teissier's<sup>18</sup> case; Teissier found them in the blood of a patient suffering from infestation of the intestines by *Strongyloides*. In the case of a general infection of a chimpanzee with larvae, Blacklock and Adler<sup>16</sup> assumed that the larvae had entered the circulation through the skin after having developed in the crevices of a wooden cage—which seems unlikely.

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18. Teissier: Contribution a l'étude de l'anguillule stercorale. De la pénétration dans le sang des embryons de l'anguillule stercorale, Arch. de méd. expér. et d'anat. path. 7:675, 1895.

Gage<sup>14</sup> pointed out that the long persistence of the disease presupposes constant reinfection, and he believed that, although in his patient reinfection from the skin was probable on account of the filthy condition, it also occurred, perhaps to a greater extent, from the intestines by way of the thoracic duct.

The discovery of the larvae in the wall of the colon and in a mesenteric lymph node in my case is important for two reasons. In the first place, it confirms Gage's idea that reinfection in strongyloidosis can take place from the intestines, and second, it explains the occurrence of colitis and diarrhea in connection with the disease. I think that a transformation of the rhabditiform embryos into filariform larvae occurs more commonly in the colon, as in my case, than in the small intestine, as in Gage's<sup>14</sup> case. Probably in the colon it is a constant occurrence. The entrance of some of the larvae into the blood vessels supplies a limited number of new mother worms, and this accounts for the indefinite persistence of the infection. When the larval invasion is unusually marked in a sensitized person colonic irritation results, followed by diarrhea. This was evidently so in my case, in which the number of filariform larvae in the mucous membrane of the colon was large. In the spots of heaviest infestation, a half dozen, at least, were present in each section which, when a similar distribution prevails over a piece of the colon of any size, means the presence of an enormous number. Only relatively few of them, however, had succeeded in entering the submucosa by penetrating through the muscularis mucosae. The majority of them were found coiled in the stroma of the mucous membrane in front of this obstacle. The unsuccessful ones probably finally die, disintegrate and are absorbed. The specimens leave no doubt as to the actual invasion of the stroma of the mucous membrane.

In the ordinary course of events the infestation persists indefinitely with occasional attacks of diarrhea or without any symptoms. When, for unknown reasons, an unusually large number of embryos within the intestinal tract change into filariform larvae and enter the intestinal wall in the region of the colon, a severe colitis with a marked infiltration of the mucosa with eosinophilic leukocytes is produced. In exceptional cases, this is accompanied by so massive a general invasion of the body with larvae that death results. From my observations and from others reported in the medical literature it would appear that sometimes under these circumstances practically all of the embryos in the intestinal contents become larvae and invade the bowel wall, with the result that not any or only a few parasites are present in the fecal discharges.

The occurrence of the severe, fatal infestations that have been mentioned in this article makes it evident that, in spite of the usual absence of alarming symptoms, strongyloidosis must be regarded as a serious

disease. It was looked on as such by Barlow,<sup>19</sup> who had the opportunity of studying a series of twenty-three cases in Central America. He described a first stage of invasion, which is usually accompanied by marked symptoms; a second, latent stage, which may last for many years and in which there are no serious symptoms while the parasites continue to be present in the stools; a third stage of diarrhea and a final stage of neurasthenia.

In my case, the attack was evidently a recurrent one, because the patient had had similar manifestations two years before when still living in Texas. It is improbable that he contracted the disease during his stay in California. His death must be directly ascribed to the infection with *Strongyloides*. A general lack of resistance due to chronic myocarditis may have contributed to the fatal outcome, but there was no evident disturbance of the general circulation, nor did he die from cardiac disease.

#### CONCLUSIONS

Strongyloidosis, although usually not accompanied by serious symptoms, may produce severe disturbances and occasionally death.

In this disease, autoreinfection takes place constantly by the entrance of filariform larvae through the skin, especially in the region of the anus, or by their invasion of the intestinal wall, usually in the region of the colon and rectum. From the colon and upper part of the rectum, the larvae are carried to the lungs indirectly by way of the thoracic duct, while those that penetrate the lower part of the rectum can reach the lungs directly by way of the lower hemorrhoidal veins. The direct mode is probably the more important one, because on the long indirect way many larvae must be destroyed before arriving in the lungs.

The diarrheal attacks are due to an inflammatory irritation of the colon caused by its invasion by the larvae. As usual in infections with animal parasites, their entrance into the tissues is accompanied by a marked local eosinophilia. In spite of the large collection of eosinophils locally, the general eosinophilia is not, as a rule, pronounced.

I have been unable to convince myself that either the mother worms or the rhabditiform embryos ever enter the stroma of the mucous membrane. They cause, however, much epithelial destruction. No evidence has been found that the mother worms become embedded permanently in the mucosa.

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19. Barlow: Clinical Notes on Infection with *Strongyloides Intestinalis*, Based upon a Series of Twenty-Three Cases, Interstate M. J. **22**:1201, 1915.

# MALIGNANT RHABDOMYOMA OF THE LEFT LEG\*

EDWIN F. HIRSCH, M.D.

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The rarity of tumors originating in striated skeletal muscle has been emphasized recently in the reports by Wolbach<sup>1</sup> and Dewey.<sup>2</sup> In considering the previous accounts of these tumors, Dewey arranged the voluntary striated muscle tumors into two groups: (1) those arising in tissues and organs that normally have no striated skeletal muscle and hence are heterotypic or teratomatous, as in the urogenital tract, the parotid gland and the lungs; and (2) those in the voluntary striped muscle, such as the tongue, lip and skeletal muscles. The latter are the rarer, and of these the frankly malignant tumors are few. The reports of such malignant tumors in man with the details of postmortem examination dwindle to a surprisingly small number. Burgess,<sup>3</sup> in 1913, described extensive metastases in the body of a woman, aged 19, secondary to a primary growth, which the author believed originated in the extensor muscles of the right thigh. He stated in this report that the only other account of a similar tumor had been recorded by Adami who found the tissues in a trout. Burgess<sup>3</sup> at that time could find no description of malignant rhabdomyoma with metastases in man. Martin and Alexander,<sup>4</sup> in 1924, published the clinical and postmortem observations of a malignant rhabdomyoma originating in the soft palate of a girl, aged 6 years. While removing the tonsils of this child, a large mass unlike adenoid tissue was discovered in the nasopharynx. The diagnosis of rhabdomyoma was made from microscopic preparations of a small portion. A more careful examination later demonstrated that the new growth had arisen from the upper and posterior portion of the soft palate. Four months after the tumor was found, the left cervical lymph glands had become enlarged and the mass in the palate had grown so as to obstruct markedly the nasopharynx. The lymph glands, the soft

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\* Submitted for publication, March 5, 1929.

\* From the Henry Baird Favill Laboratory and the Surgical Service "A" of St. Luke's Hospital.

\* Aided by the Winfield Peck Memorial Fund.

1. Wolbach, S. B.: A Malignant Rhabdomyoma of Skeletal Muscle, Arch. Path. **5**:775 (May) 1928.

2. Dewey, K. W.: Rhabdomyoma of the Tongue, Arch. Path. **3**:645 (April) 1927.

3. Burgess, A. M.: Malignant Rhabdomyoma with Multiple Metastases, J. M. Research. **29**:447, 1913-1914.

4. Martin, G. E., and Alexander, W. A.: A Case of Rhabdomyosarcoma of the Soft Palate, J. Laryng. & Otol. **39**:312, 1924.

palate and the regional extensions around the eustachian tube were removed surgically. Three weeks later, an aural polyp was excised. Treatment with radium failed to stem the progress of the tumor and death occurred six months after the growth was discovered in the soft palate. While the tissues which were first removed and examined contained structures that Martin and Alexander<sup>4</sup> considered to be of muscular origin, those removed later had the appearance of a spindle cell sarcoma but also included cells which were thought to be of muscular origin. According to their statements, Martin and Alexander<sup>4</sup> would have been unable to establish the muscular origin of this tumor had not the tissues originally removed surgically been available. Additional information obtained by postmortem examination was not included in their report. They referred, also, to a rhabdomyosarcoma of the nasopharynx described by Richardson.<sup>5</sup>

Among the nine cases accepted by Küttner and Landois<sup>6</sup> as rhabdomyomas of skeletal muscle, those reported by Ribbert,<sup>7</sup> Zenker (Bayer)<sup>8</sup> and Fujinami<sup>9</sup> seemed to be definite instances of a malignant growth, because of either recurrence or histologic structure interpreted by the authors as malignant. These reports, however, are based only on the study of tissues obtained surgically. Other accounts of malignant skeletal rhabdomyomas in tissues removed surgically are by Muller,<sup>10</sup> Nicory,<sup>11</sup> Wolbach<sup>1</sup> and Wagner.<sup>12</sup> The tissues studied by Muller<sup>10</sup> were from the right thigh of a man, aged 48; those studied by Nicory,<sup>11</sup> from the uvula of a girl, aged 5 years; the ones by Wolbach,<sup>1</sup> from the dorsal muscles of the chest of a girl, aged 4 years, and those by Wagner,<sup>12</sup> from the right buttock of a man, aged 40 years. The ultimate fate of the patients from whom the tissues were removed was not stated in any of these accounts except Wolbach's; in this instance death occurred after three months. The mixed tumor of the triceps

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5. Richardson, in von Bermann: *System of Surgery*, 1904, vol. 1.

6. Küttner, H., and Landois, F.: *Die Chirurgie der quergestreiften Muskulatur*, *Deutsche Ztschr. f. Chir.* **25**:1, 1913.

7. Ribbert: *Beiträge zur Kenntniss der Rhabdomyome*, *Virchows Arch. f. path. Anat.* **130**:249, 1892.

8. Zenker, K.: *Ein Fall von Rhabdomyosarcom der Orbita*, *Virchows Arch. f. path. Anat.* **120**:536, 1890.

9. Fujinami, A.: *Ein Rhabdomyosarcom mit hyaliner Degeneration (Cylindrom) im willkürlichen Muskel*, *Virchows Arch. f. path. Anat.* **160**:203, 1900.

10. Muller, H. R.: *Traumatic Rhabdomyosarcoma Following Successive Fractures of the Femur*, *J. Cancer Research* **2**:393, 1917.

11. Nicory, C.: *Rhabdomyoma of the Uvula, with a Collection of Cases of Rhabdomyoma*, *Brit. J. Surg.* **11**:218, 1923-1924.

12. Wagner, J. H.: *Rhabdomyosarcoma of the Buttock*, *Atlantic M. J.* **31**:570, 1928.

muscle of the right arm reported by Johan<sup>13</sup> was considered by him to have arisen in misplaced somatopleura. Reference is made in this account to reports of similar tumors by Buhl, F. Marchand, Mohr and Lambl.

Burgess<sup>3</sup> described the tissues in his tumor as composed of cells with large vesicular nuclei and a relatively small amount of cytoplasm, about the size of a polymorphonuclear leukocyte. Many were in mitosis. In certain places there were large cells, some multinucleated and containing a large amount of acidophilic cytoplasm. These cells ranged in size between three and six times the diameter of a leukocyte; the nuclei were grouped along the periphery. Among the tapering cells with longitudinal fibrils were some with cross-striations. Burgess stated that he experienced some difficulty in demonstrating cross-striations in the cells. Martin and Alexander,<sup>4</sup> in their report, said that the first tissues removed were myxomatous, but that fibers were included which differed only a little from adult skeletal muscle cells, and that there were many spindle-shaped cells with acidophil cytoplasm and long-tailed ends. Large cells, frequently multinuclear, varying greatly in size, shape and staining reaction, were outstanding structures. Some of these resembled a tadpole in shape, with several nuclei in the "head" and abortive striations of the "tail." Others were round or oval and contained as many as seven round or oval nuclei. The tissues removed later had the structure of a spindle cell sarcoma, but certain cells were differentiated somewhat into muscle fibers.

The tissues described in the earlier accounts (Ribbert, Zenker and Fujinami) contained spindle-shaped cells with cross-striations, as did those reported by Nicory. The tumor recorded by Muller had interlacing bundles of long fusiform cells resembling skeletal muscle and many mononuclear or multinuclear giant cells. Cross-striations were not demonstrated. Wolbach found spindle cells with definite cross-striations in the tumor that he described. He suggested that the myofibrils originate in the centrioles, and that in the absence of definite cross-striations, these tumors may be identified by establishing the presence of centriole clusters and abortive formations of fibrils.

The following account is distinctive in that the myogenic nature of the tumor was recognized in metastases of lymph glands removed several months before the patient died, and because extended observations were made of the disease in many parts of the body by post-mortem examination and subsequent histologic studies.

#### REPORT OF CASE

J. B., aged 6½ years, was admitted to the surgical service of Dr. L. L. McArthur on June 6, 1928, because of a painful, hard, uncircumscribed swelling

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13. Johan, B.: Ein Rhabdomyosarcoma Chondro-myxomatosum des Oberarmes, Frankfurt. Ztschr. f. Path. **22**:50, 1919.



in the muscular attachment of the left achilles tendon, and a mass the size of a hen's egg in the left groin. The parents made an indefinite statement concerning a bruise of the leg in July, 1927. About that time, however, a hard mass in the leg was first noted. A physician regarded this as a hematoma, but tissues removed in December, 1927, were diagnosed sarcoma. In April, 1928, the mother noticed a firm mass in the left groin which progressively increased in size. For about two weeks before admission, the boy complained of pain in the left leg, and the mother thought the leg had increased in size. The notes on the physical examination made June 6, 1928, include no important details, except mention of the firm enlargement of the left leg and the mass in the left groin. This mass was removed on June 23, 1928. It was ovoid, encapsulated and 5 by 3 by 2.5 cm. The surfaces made by cutting were white, opaque, firm tissue, mottled somewhat by faintly yellow regions (necrosis) about 1 mm. in diameter.

*Histology of the Lymph Gland Tissue.*—A stroma of delicate fibrous connective tissue formed the supporting framework of the tumor. In the compact portions, the cells between the stroma fibrils were from 10 to 15 microns in diameter. They had large, oval or indented vesicular nuclei with several coarse chromatin granules, and only a narrow margin of granular cytoplasm. These cells were definitely arranged around capillaries which, with the intimately arranged stroma, accompanied the cells in all parts of the tumor. In less compact portions, especially near necrotic foci, there were large round or oval cells, from 30 to 40 microns in diameter with a granular acidophilic cytoplasm and a single, large round or oval vesicular nucleus, or several nuclei not as large, without regular distribution. Along the edge of the cytoplasm was a narrow layer of refractile substance resembling the ectoplasm of an ameba. The finer details of the structure of the cytoplasm varied considerably. The cytoplasm of some cells contained a few coarse basophilic granules or fine threadlike structures, while that of other cells was drawn out into long slender or short plump prolongations with fine longitudinal striae mottled with alternating delicate light and dark bands like the cross striations of skeletal muscle fibers. These cross striations were especially distinct in large spindle-shaped cells, as long as 170 microns (fig. 1). The single large vesicular nucleus with coarse chromatin granules, usually in the center of the fiber, made an abrupt nodal enlargement of the cell. Short segments of fibrils with cross striations were found without regularity in a variety of places, representing, no doubt, portions of cells the nuclei of which were not in the plane of the sections. Bands of protoplasm were found suggesting skeletal muscle fibers, 70 microns long and from 15 to 20 microns wide, with several nuclei arranged along the periphery. Many cells in mitosis were found. Certain of the finer details of cell structure mentioned were demonstrated in a striking way in sections stained with phosphotungstic acid-hematoxylin.

Because of the presence of these fibrillar structures with cross-striations in tumor tissues metastatic in a lymph gland, a place where one does not regularly find skeletal muscle fibers and which, if present, might alter the conclusion that the spindle-shaped structures mentioned were tumor cells and not inflammatory or retrogressive changes of the skeletal muscle ingrown with tumor, the diagnosis "metastatic rhabdomyosarcoma of the groin lymph glands" was made. The blood on June 9, 1928, had 3,500,000 erythrocytes and 7,600 leukocytes per cubic millimeter, and the hemoglobin was 65 per cent. Dr. E. L. Jenkinson reported, from roentgen films, some destruction of the left os calcis, but no shadows that suggested a growth from the bones. The patient received roentgen treatments and was discharged from the hospital on July 11, 1928, but returned from time to time for further radiation therapy. On Oct. 29, 1928, he was readmitted. The left leg had

swollen so that it was three or four times as large as the right. The left leg was hard and in the upper part of the thigh was a firm mass that extended into the inguinal region. A loss of 6 pounds in weight had occurred. The blood on Oct. 30, 1928, contained 3,310,000 erythrocytes and 7,150 leukocytes, and the hemoglobin content was 63 per cent. On Nov. 29, 1928, Dr. Jenkinson reported definite changes of both lungs, especially of the left lower lobe in roentgenograms, which he interpreted as tumor metastases. There was a slight daily fever ranging between 98.8 and 100 F.; it was somewhat higher during the three days before Nov. 27, 1928, when the patient was taken home for a few days. He returned on Nov. 30, 1928, without appreciable change in his physical condition. The left leg increased in size, tumor nodules appeared in the tissues of the abdominal wall, and apathy, weakness and emaciation increased until death on Jan. 16, 1929, at 12:25



Fig. 1.—A large spindle-shaped cell with cross-striations found in the groin lymph gland removed during life;  $\times 1,730$ .

a. m. Postmortem examination of the trunk and left leg was made eight hours later. The essential features of the anatomic diagnosis are: huge primary rhabdomyosarcoma of the left leg with marked extension into the left thigh; extensive metastases of the inguinal, pelvic, periaortic, mesenteric, retroperitoneal, biliary, perisplenic, mediastinal, peribronchial, and left axillary lymph glands, and of the lungs, the urinary bladder, the abdominal wall, the skin of the penis and scrotum, and the tissues of the left side of the chest; sarcomatous erosion of the ramus superior of the left os pubis and of the left fibula; bilateral hydronephrosis and hydroureter; marked edema of the left leg and thigh and slight edema of the right; sarcomatous ulcerations of the lining of the inferior vena cava; marked dilatation of the superficial veins of the chest; bilateral hemorrhagic hydrothorax, and marked emaciation.

Only the pertinent statements of the descriptive portions of the postmortem record are included. The hugely enlarged left lower extremity, flexed at the knee, had a diameter of 18 cm. in the middle of the thigh and a dorsoventral thickness of 17 cm. in the center of the leg. The corresponding dimensions of the right lower extremity were 11 and 7 cm., respectively. The skin of the left leg was tense and pebbled like hog's skin; that of the thigh was elevated by many subcutaneous nodules of tumor tissue ranging in size up to 25 mm. in diameter. In the lower three fourths of the thigh these were confluent, but in the upper one fourth they were discrete. Their distribution was chiefly along the front, medial and lateral portions of the thigh. A region of skin tissue 11 by 17 cm. on the front and inside of the middle of the thigh was ulcerated. The nodules in the subcutaneous tissues and skin extended nearly to the costal arch on the left side of the abdomen. They involved the scrotum, the shaft of the penis and the right groin. The superficial veins of the front of the chest, were markedly dilated. There were several enlarged lymph glands in the base of the left axilla near the anterior border. The subcutaneous fat in the midline of the trunk was practically absent. In the front midline incision beginning 4 cm. above the umbilicus and extending down to the symphysis pubis were discrete masses of soft white tissue as large as 2 cm. in diameter, making an almost continuous chain, those below having the largest dimensions. The lymph glands of the right axillary fossa were small but in the left, as noted, were several enlarged glands, in all a mass 5 by 3.8 by 2 cm. Some of these were grayish-pink lymphoid tissue with discrete masses of white tumor substance. Extending up from the small pelvis in the midline and lying chiefly on the left side was a mass of soft white tumor tissue 9 by 8 by 6 cm. It occupied a position corresponding to the urinary bladder and was continuous on the left side into the groin. The rectum and sigmoid colon were behind and not attached, although the rectum was markedly compressed. The tissues of the left groin were extensively ingrown with tumor tissue; those of the right, less extensively. The spleen was not enlarged. In the omental fat near the hilum were small masses of white tumor tissue as large as 1 cm. The mesenteric lymph glands were not enlarged. In the periphery of the abdominal surface of the right leaf of the diaphragm were a number of small, flat, pearly thickenings, but there were none in the left half. A small amount of bloody fluid was found in the right pleural cavity, about 200 cc. in the left. There were no adhesions between the parietal and visceral pleura. In the region of the thymic body were two masses of pinkish-white tissue, the left mass 4.5 by 3.3 by 2.2 cm., the right 3.3 by 3 by 2.2 cm. Some portions of these were dark red with recent hemorrhages. Careful examination of the ribs after the chest and abdomen had been eviscerated failed to disclose tumor masses in them but in the soft tissues just below the tip of the left twelfth rib was a mass 1.5 by 1.5 by 1 cm. The lining of the thoracic duct was smooth; the lumen was about 1 mm. in diameter. In the upper thoracic levels in close approximation to the thoracic duct channel was a tumor mass 3.5 by 1.5 by 1.5 cm. The lining of the receptaculum chyli was smooth but the lumen was dilated; it was embedded in masses of lymph glands markedly enlarged by tumor tissue. The thoracic, and especially the abdominal, periaortic lymph glands, were markedly enlarged by tumor tissue and, with tissue in the small pelvis, they formed a huge pyramidal-shaped mass 16 cm. long, 9 cm. wide and 4 cm. thick at the base. They were directly attached to the periosteum of the spinal vertebrae and did not penetrate the bone tissues here. Most of the superior ramus of the left os pubis, however, was destroyed. The parabronchial lymph glands, and the biliary, and peripancreatic lymph glands were markedly enlarged and ingrown with tumor tissue. At the upper pole of the left kidney in

the fat was a pyramidal-shaped, discrete mass of tumor tissue 3.8 by 3.5 by 2 cm. The right lung weighed 180 Gm. The pleura was glistening and smooth. The outlines of the lung lobules were traced in fine black lines of carbon pigment. The lung substance proper was grayish pink and fluffy, except in many discrete nodular regions containing grayish-white tumor tissue, ranging from a few millimeters to 2.5 cm. in diameter and forming about 50 per cent of the entire lung substance. The left lung weighed 400 Gm. and was much more extensively consolidated by tumor tissue. At least four fifths of the lower lobe was solid with tumor, and in the upper lobe were many discrete nodules as large as 1 cm. in diameter. Both lungs were inflated and fixed in formaldehyde. After hardening they were bisected in a plane through the hilum to the periphery. The lower portion of both ureters was greatly compressed by the pelvic tumor tissues and the portions of ureters above were markedly dilated as were both renal pelves and

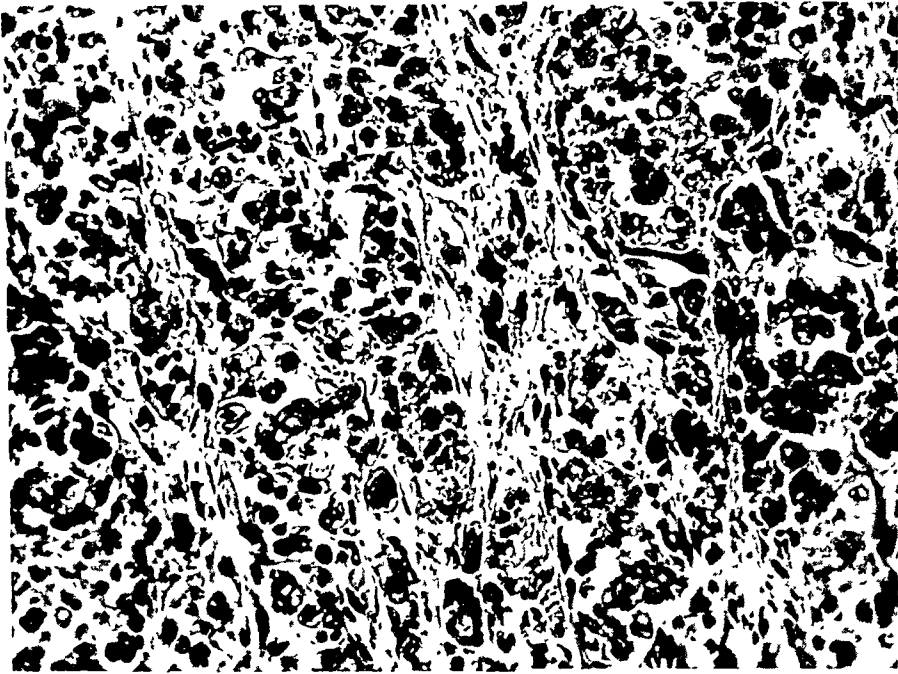


Fig. 2.—The metastatic tumor tissue in a parabronchial lymph gland, illustrating the compartments formed by connective tissue septums, the arrangement of cells along these septums and the variations in the size and shape of the cells;  $\times 151$ .

the major and minor calices of the kidneys. The right kidney without the capsule and pelvic fat weighed 70 Gm., the left, 60 Gm.

The wall of the urinary bladder was markedly ingrown with white tumor tissue. The inferior vena cava was encased in the enlarged periaortic abdominal lymph glands, and in two places, 3 and 5 mm. in diameter, in the lower portion in front the wall was ulcerated.

On the surfaces made by a deep incision in the front of the left thigh from the groin to the knee and continued through the left leg there was no red muscle tissue, but instead the entire soft parts were lobulated soft white tumor tissue, wet with huge quantities of serous fluids. The shafts of the femur and of the tibia were smooth; the fibula was roughened and eroded.

In the detailed procedure of the necropsy, careful examinations were made of other structures such as the azygos and innominate veins, the aorta and its large

branches, the heart structures, the superior and inferior cavae and their branches, the pulmonary artery and veins, the suprarenal glands, the bile ducts and gall-bladder, the portal vein and its tributaries, the pancreas and its duct, the spleen, the liver (no metastases), the esophagus, the stomach, the small and large bowel (opened lengthwise), the rectum, the appendix vermiformis, the testes, the prostate, the seminal vesicles, the urinary bladder and the bones in general. The head and neck were not opened. Certain of the tissues of the neck were inspected from below; palpation revealed no enlarged cervical lymph glands.

*Histology.*—Paraffin sections were prepared of tumor tissues in the left leg and thigh, the metastases of the parabronchial, peripancreatic, periaortic and left

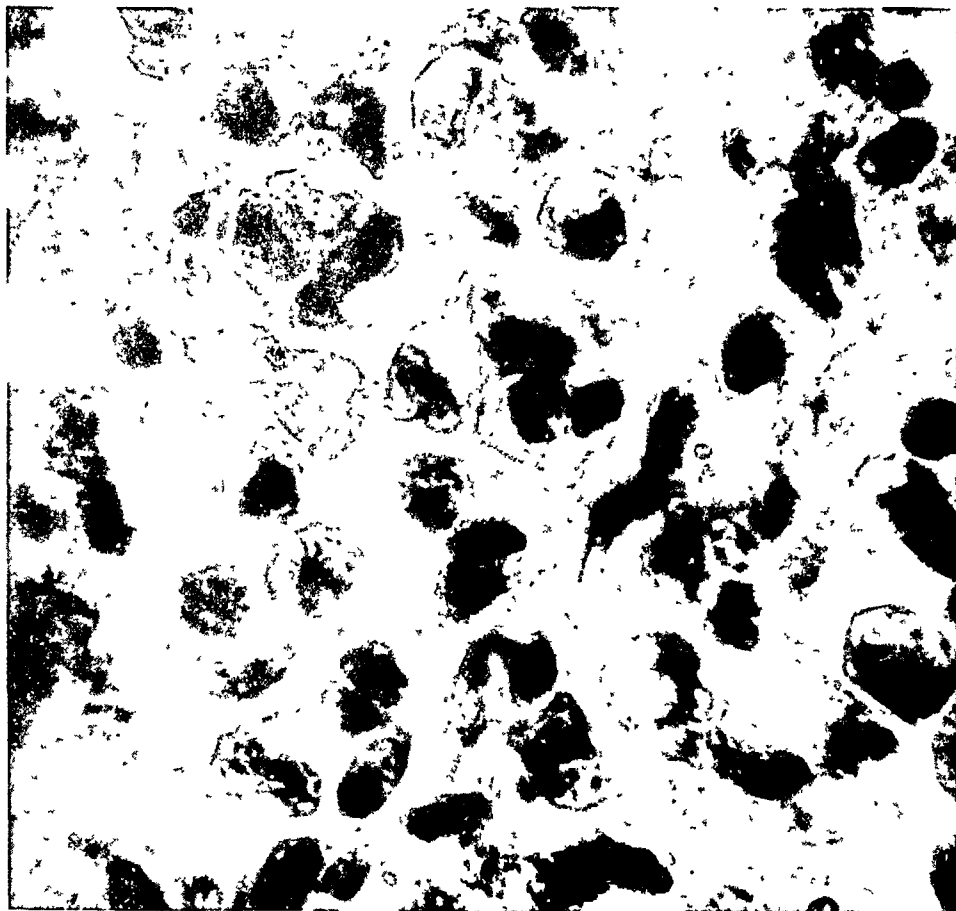


Fig. 3—Some of the cellular portions of tumor tissue containing chiefly large round cells. Much glycogen was contained in the cytoplasm of such cells,  $\times 1,200$ .

axillary lymph glands, of the secondary growth near the left kidney, of the left lung and of the nodules in the midline incision of the abdomen. These sections were stained with hematoxylin and eosin, and with phosphotungstic acid-hematoxylin. There was little difference in the tumor tissues in the various sites. The variations were largely in the proportion of the various cellular constituents, the amount and arrangement of the accompanying stroma, and the changes caused by edema or necrosis. Metastases in certain of the lymph glands lend themselves best to the description because the changes due to edema and necrosis were absent; for this reason, the structure of the metastases in the parabronchial lymph glands is given as representative of the tumor.

The structure of the lymph glands was completely replaced by tumor tissue. The more obvious supporting fibrous stroma was in narrow bands, so arranged and interwoven as to form compartments 0.1 mm. and less in diameter resembling the coarse pattern of lung tissue (fig. 2). Small capillaries extended through these narrow collagenic connective tissue septums. In some places this pattern of delicate connective tissue septums had a marked resemblance to the stroma of a highly papillary epithelial growth. Within the compartments were masses of cells, compactly or loosely arranged. They varied considerably in size and shape, not only within each compartment, but in these descriptive units, in various parts of the tumor. Round, oval or elongated cells were the most common, many about 15 microns in diameter, some smaller and others slightly larger (fig. 3). They had an abundant acidophilic, granular cytoplasm, and usually a single large vesicular nucleus, round, oval, indented or lobed, with coarse chromatin granules. Because

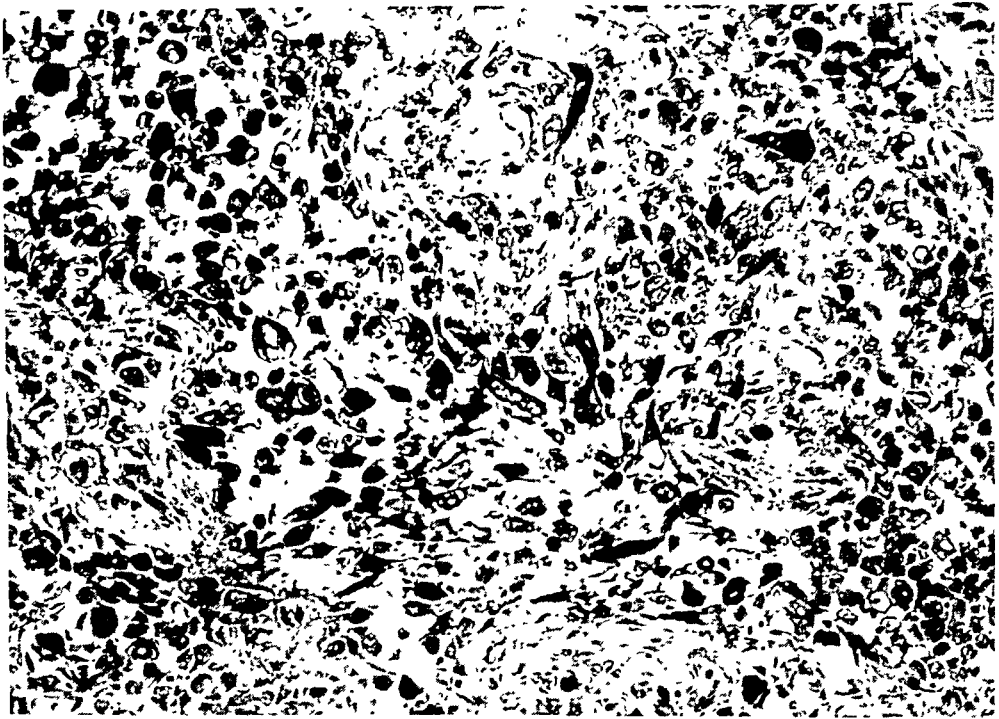


Fig. 4.—Tumor metastases in the lower lobe of the left lung. A number of large protoplasmic masses are included;  $\times 151$ .

of considerable variation in contour it seemed probable that these cells had third dimensions unequal to the other two and tended to be cylindric. This belief was strengthened by the presence of elongated protoplasmic masses with fine longitudinal striae, wider at one end than at the other, the broad end enclosing the nucleus. A layer of cells was usually in direct continuity with the vascular septums, some closely approximated with a broad attachment to the stroma or extending away like a pallisade at right angles, the nucleus at the distal end of an elongated cell, and the proximal portion like a pedicle, narrow at the base (fig. 2). Among these cells that were closely applied to the fibrous septums were several cells, 40 microns and more in length, elongated and spindle-shaped, like segments of developing muscle fibers (fig. 4) with delicate longitudinal fibrils and cross-barred striations just like the bands of skeletal muscle fibers. There was little, if any, appreciable fibrous stroma between the cells. In addition, there were

cells with a short tapering end like a "comet," the nucleus at the broad end; round cells with centrally placed vesicular nuclei, having in their cytoplasm concentrically arranged fibrils with segmented granules like cross striations and, in the nucleus, many small threadlike filaments; and large oval acidophilic masses of cytoplasm with a marginal border like a sarcolemma and many small irregular vesicular nuclei arranged peripherally. Among the septums were isolated fibrils and small bundles of fibrils like a delicate tracing of fine lines with alternating light and dark segments. In the tissues from the left thigh and leg, especially where edema was marked, most of the cytoplasm and nuclear structures of certain cells had disappeared, leaving only narrow rings, structures which corresponded in a general way to the sarcolemma of skeletal muscle fibers. Tissues from the primary tumor and from many of the metastases fixed in absolute alcohol were stained for glycogen. All of these tumor tissues contained many cells with glycogen granules.

The microscopic examination of the spleen, liver, kidney, myocardium, pancreas, esophagus, aorta, testes, epididymides, accessory splenic nodule, gallbladder, stomach, small bowel and trachea disclosed no additional features of interest. The nodular masses in the right leaf of the diaphragm were tumor tissue with a predominance of the smaller variety of cells like large round cells, but they included also a number of larger cells with acidophilic cytoplasm. The bone tissues of the ramus superior of the left os pubis were extensively destroyed by tumor.

#### COMMENT

The tumor described originated, no doubt, in skeletal muscle of the left leg. This conclusion follows because in all metastatic tissues removed during life or examined post mortem, cells were found which were primitive or abortive muscle structure, containing acidophilic cytoplasm, an ectoplasm resembling a sarcolemma, one or more vesicular nuclei, and concentric fibrils with alternating light and dark bands or protoplasmic prolongations having longitudinal fibrils and cross-striations like the light and dark bands of skeletal muscle. The cells in all of the areas of metastasis examined contained large quantities of glycogen.

# INGUINAL LYMPHADENITIS

WITH SPECIAL REFERENCE TO THE GROUP KNOWN AS  
CLIMATIC BUBO \*

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About two years ago there was received at the Hygienic Laboratory of the U. S. Public Health Service a lymph gland which revealed a picture unlike any of the usual adenopathies, but resembling closely the picture for climatic bubo described in the literature. Since that time a number of similar cases have been studied, and also a number of histologically dissimilar cases of adenitis diagnosed clinically as climatic bubo. As microscopic descriptions of the condition have been few, and as some of these cases showed a close correspondence to the microscopic changes described in cases of climatic bubo, they are deemed worthy of reporting.

Letulle and Nattan-Larrier<sup>1</sup> studied a case of bubo of some months' duration in a young Costa Rican. This gland showed some normal follicles, and a much diffuse, disordered area in which the follicles and sinuses had disappeared and in which, in the meshes of the reticular tissue, lymphocytes and an excessive proportion of plasma cells were seen, with here and there plasma cell nodules. The gland also showed distention of the blood vessels with margination and emigration of polymorphonuclear leukocytes; foci of necrosis with pyknosis and karyorrhexis, hyalinization and increased vividness of staining of the cytoplasm; and numerous polymorphonuclear leukocytes and other phagocytes nearby.

Foci of suppuration were also seen showing disorganized tissue distended with polymorphonuclear leukocytes, some of which were partially disintegrated.

Recent and old hemorrhagic foci were seen, the latter with hemosiderin. The periglandular vessels showed perivascular mesovascular and endovascular infiltration with round cells.

Thickening and general increase of fibrous tissue were observed, with infiltration of the interstices with plasma cells and lymphocytes. There were intracellular inclusions in plasma cells near the necrotic foci. These were ovoid, measuring from 4 to 5 microns by 3 microns,

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\* Submitted for publication, March 1, 1929.

\* From the Hygienic Laboratory, U. S. Public Health Service.

1. Letulle, M., and Nattan-Larrier, L.: Bull. Soc. path. exot. **3**:755, 1910.



and containing two unequal chromatic granules. These inclusions were considered as possibly nuclear *débris*, possibly parasitic. None of the usual bacterial stains revealed recognizable organisms.

Müller and Justi<sup>2</sup> described the pathologic changes in two cases. The first presented several large, tense glands with thickened capsules. The cut surface was light grayish red, with several irregularly disposed necrotic foci, some with abscess cavities. The periglandular fatty tissue showed dilated vessels and some swollen septums infiltrated with large cells with pale vesicular nuclei containing acidophilic nucleoli and granular or vacuolated cytoplasm. The cells formed a reticulum with their prolonged processes. In the meshes were seen numerous lymphocytes, polymorphonuclears and red cells. Numerous mitoses were present. Some fibrin was found. The gland capsule showed young fibroblasts, numerous erythrocytes, lymphocytes and plasma cells.

The gland substance showed many blood vessels. The capillaries especially showed endothelial swelling and proliferation, and near the necrotic foci hyaline thrombi. The dilated vessels contained neutrophil leukocytes in the lumen and in their walls. The normal gland structure was obliterated.

In some areas there was marked proliferation of the reticulum with large nuclei and numerous mitoses. In the meshes were lymphocytes and plasma cells, the latter with from one to six nuclei, also cells with large nuclei and narrow cytoplasm (endothelium cells) and numerous transitional forms between these and the plasma cells. Mitoses were frequent in all these cells. In some areas the lymphocytes predominated, in others the plasma cells. In some places there were numerous erythrocytes.

Near the necrosis there was proliferation of the reticulum cells and endothelium cells to form new connective tissue, the cells taking on the appearance of young fibroblasts. Here the meshes were narrower and contained lymphoid cells in smaller numbers.

The necrotic foci were either sharply demarcated or set off by a marginal zone in which the nuclei of the reticular and endothelial cells persisted, often elongate like the palisade cells in a gumma. Polymorphonuclears, lymphocytes and plasma cells were also found in this zone. In the necrotic areas proper, the reticulum might or might not be recognizable. Nuclear fragments of all sizes were seen, as well as cytoplasmic *débris*. Necrotic leukocytes were seen. Here and there was evidence of calcification.

There was widespread deposit of either hyalin or fibrin, especially about capillaries and near the necrotic foci.

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2. Müller, O., and Justi, K.: *Beihfte z. Arch. f. Schiffs- u. Tropen-Hyg.* 18:857, 1914.

A few bacteria were found in one section in the margin of an area of necrosis. These were short, fat, club-shape rods, mostly extracellular, but occasionally in an oval vacuole in a reticulum cell. The free bacteria stained violet with Giemsa.

Their second case showed greatly hypertrophied germinal centers appearing almost like tubercles under low magnification. There were close packed vesicular nuclei. Many mitoses were present. Some cells showed beginning karyolysis, others complete fragmentation of the nucleus. The cytoplasm of the necrotic cells coalesced into a finely granular mass containing nuclear fragments. A few polymorphonuclear leukocytes were found about these foci of necrosis. Bacteria resembling those seen in the first case were also seen in this.

Stefko <sup>3</sup> described briefly two cases in which blood cultures produced *Staphylococcus aureus*. The first showed an acute lymphadenitis, the second a chronic fibrous lymphadenitis with numerous plasmacytes, fibroblasts and abundant connective tissue. This case showed also *Plasmodium malariae* in the blood.

Castellani and Chalmers <sup>4</sup> stated that the capsule of the gland is much thickened, interstitial tissue is abundant, there is great proliferation of lymphocytes, hemorrhagic foci occur here and there and numerous plasma cells are present.

Whitmore's <sup>5</sup> paper on climatic bubo contains brief histologic descriptions of four of his cases:

CASE 1.—Sections show a thickened capsule and marked fibrosis throughout the tissue. The germinal centers are well defined and enlarged. The medullary sinuses and blood vessels are distinctly dilated and full of fluid. Numerous areas of leukocytic infiltration are seen, being especially evident in the cortex. In many of the germinal centers small abscess formation has developed.

CASE 2.—Sections show the entire gland to be the seat of acute inflammatory reaction associated with vast areas of necrosis and localized abscess formation.

CASE 9.—Chronic inflammation and abscess formation; no evidence of specific or tuberculous infection.

CASE 10.— . . . sections showed marked proliferation of germinal centers in peripheral parts of glands, with multiple necrotic foci in central parts; marked periglandular inflammation with round cell infiltration. . . .

Hanschell <sup>6</sup> found no constant histologic differences distinguishing the morbid changes in climatic bubo from those seen in genital scabies or ulcus molle.

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3. Stefko, W.: Bull. Soc. path. exot. **10**:724, 1917.

4. Castellani and Chalmers: Manual of Tropical Medicine, New York, William Wood & Company, 1919.

5. Whitmore, W. H.: U. S. Nav. M. Bull. **25**:89, 1927

6. Hanschell, H. M.: Lancet **211**:276, 1926

Günther<sup>7</sup> described gross capsular thickening and multiple small abscesses; histologically necrosis bordered by radially disposed epithelioid cells in a broad zone, reactive proliferation of the reticulum, fibrinous inflammation; in earlier stages, a thickening of the fibers of the reticulum, which were broken down in and near the necroses; later diffuse conversion of the reticulum into collagen and resulting diffuse fibrosis. The cell inclusions described earlier by this author he now considered as probably nuclear or cellular débris rather than parasitic.

Uribe<sup>8</sup> described the characteristic infiltration with large numbers of plasma cells; formation of granulomas with epithelioid margins and amorphous centers; stellate abscesses with similar walls and contents of polymorphonuclear leukocytes and large mononuclear cells; obliterating endarteritis and hemorrhages, both in capsule and in parenchyma. Giant cells of undescribed type, occurred in the infiltrated tissues. Some glands showed simple hyperplasia and congestion, with occasional small hemorrhages.

Sections from the material remaining on hand at the Hygienic Laboratory from Barber and Coogle's<sup>9</sup> case show marked hyperplasia and proliferation of the reticulo-endothelium, diffuse infiltration of the rest of the gland pulp by small lymphocytes, a densely fibrous capsule, with only a few thickened vessels and an occasional patch of infiltration with round cells, an entire absence of focal hemorrhage or necroses and absence of areas of infiltration with plasma cells. This material does not, as Hansmann<sup>10</sup> said, resemble the nontuberculous granulomatous lymphadenitis described by him; neither does it, in my opinion, resemble that in the cases described by Müller and Justi.

The other references that were available contained either nothing bearing on the microscopic changes or citations only.

#### REPORT OF CASES

CASE 1.—G. E., aged 39, a white marine fireman, on July 9, 1926, while in Galveston, Texas, struck himself in the left groin with an iron bar. There was an excruciating pain at once, and soon after a swelling in the left groin, which remained painful.

This was the patient's first and only excursion into the tropics, all previous service having been on the Great Lakes. He was admitted to the Marine Hospital at Ellis Island, New York, on July 22. There was no evidence or history of venereal disease. He had a temperature of from 99 to 100 F. for the first week in the hospital. Adenectomy was done on July 30. Grossly, the glands were friable and not encapsulated. The cultures gave no growth.

7. Günther, Reinhard: Arch. f. Schiffs- u. Tropen-Hyg. **29**:546, 1925.

8. De Bellard, E. P., and Uribe, Cesar: Gac. méd. de Carácas **32**:100, 1926 (cf. pp. 106-108, particularly); de Bellard, E. P.: J. Trop. Med. **29**:103, 1926.

9. Barber and Coogle: U. S. Pub. Health Rep. **42**:1306, 1927.

10. Hansmann, G. H.: Surg. Gynec. Obst. **39**:72 (July) 1924.

Histologically, there were diffuse fibrosis and infiltration with plasma cells, foci of necrosis, small abscesses, small hemorrhages and well marked periadenitis.

The areas of fibrosis varied from dense fibrous tissue to loose connective tissue with many large fibroblasts having large, oval leptochromatic nuclei and in the interstices numerous plasma cells and a few lymphocytes. Among them were large, deeply staining syncytial masses with sharply rounded margins and from two to five nuclei the chromatin of which lay in radially disposed coarse blocks and about the periphery. In one instance, a typical plasma cell was in contact and apparently partly fused with such a syncytium. Occasional plasma cells were in mitosis.

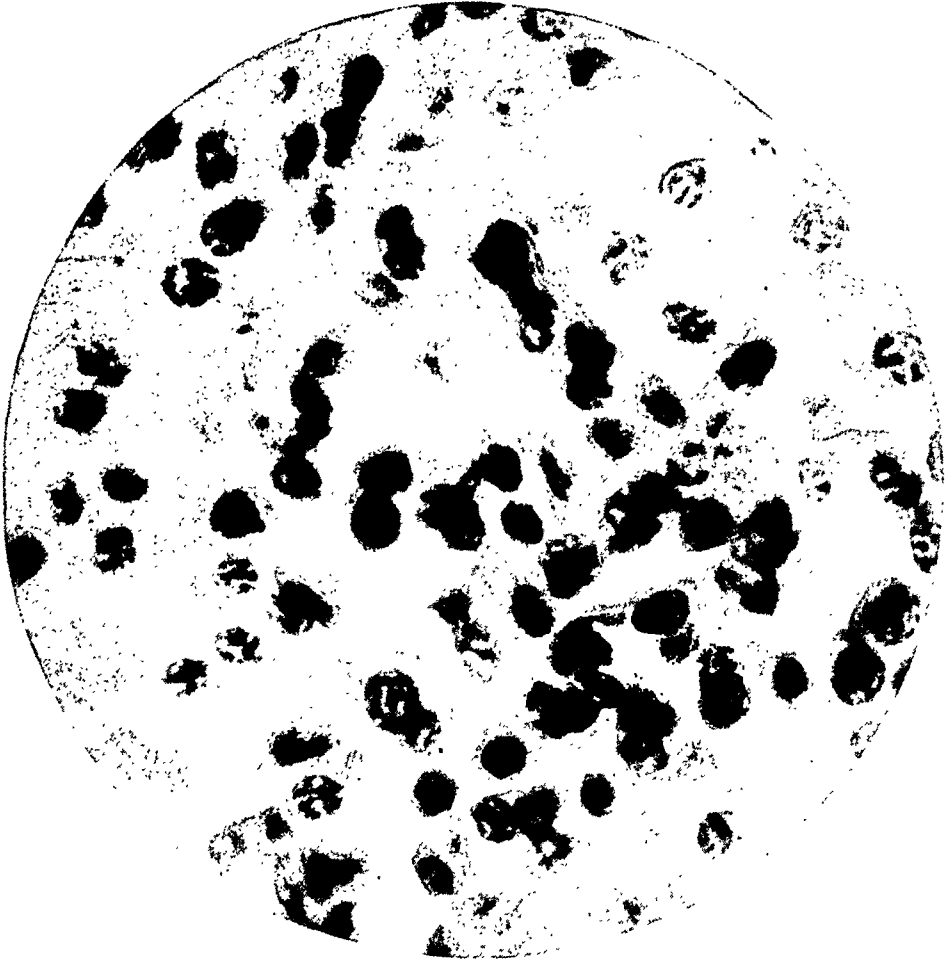


Fig. 1.—A plasma cell nodule in case 1. Hematoxylin eosin. Zeiss 60X. 1.4 N. A. Homal IV. 1,000 diameters, reduced in reproduction two-thirds.

The focal lesions consisted of large, swollen, oxyphil, poorly defined reticulum cells with well stained nuclei. In the centers of such nodular lesions, one found pyknotic nuclei and nuclear fragments either alone or with greater or less numbers of polymorphonuclear leukocytes, many of which showed disintegration and nuclear fragmentation.

About the margins of these focal lesions were found lymphocytes and plasma cells with pyknotic nuclei, considerable numbers of polymorphonuclear leukocytes and sometimes nodular accumulations of small plasma cells.

The hemorrhages were of variable age, some showing well formed red cells in the tissue adjacent to a dilated capillary; others, indistinct and malformed red

cells and many yellowish-brown pigment granules free and filling the cytoplasm of cells, some of which possessed the vesicular leptochromatic nuclei of the macrophages, others the characteristic heavily stained cartwheel nuclei of the plasma cells.

Some of the capillaries were dilated, showing margination and emigration of leukocytes. Others near by were small and contained few leukocytes. The margination and emigration were apparently not related to the nearness of foci of necrosis or abscesses.

Parts of the tissue showed normal germinal centers. Other areas resembling germinal centers showed nuclear pyknosis and fragmentation in the center, occasional polymorphonuclear leukocytes and, near the periphery, a few typical plasma cells among the lymphocytes.

In places, the capsule and, to a less extent, the surrounding fatty tissue were infiltrated with lymphocytes and plasma cells.

CASE 2.—S. M., aged 21, a negro seaman (scaler), entered the Marine Hospital at Norfolk on Feb. 26, 1927, with swollen, slightly painful inguinal glands, about three days after the onset of the symptoms. The temperature ranged around 101 F. The swelling increased. On March 7, the left side was incised and drained. The fever persisted, and the glands continued to enlarge. On March 17, the left inguinal glands were excised. Following excision there was free drainage, with prompt subsidence of the fever and clinical improvement. The condition on the right side subsided without surgical intervention.

The blood count on March 31 showed a moderate anemia (3,280,000) and a white cell count of 9,000 with relative lymphocytosis (49 per cent small, 2 per cent large lymphocytes). Cultures and smears from the wound, taken about March 31, showed gram-positive cocci and gram-negative extracellular and intracellular diplococci. There were no Donovan bodies.

Histologically, the glands removed on March 17 showed foci of necrosis, with or without polymorphonuclear infiltration, hemorrhages, areas of coagulated edema, areas of infiltration with plasma cells and of proliferation of fibroblasts and early fibrosis, complete disappearance of germinal centers and mitoses in large lymphoblasts or reticulum cells. There was a periadenitis with hemorrhages and infiltration of the capsular tissue with plasma cells and lymphocytes.

The cultures and smears were unfortunately not made until two weeks after the second operation, and their significance seems at least doubtful.

Clinically, there was no evidence of gonorrhea. The patient had had a chancre of the glans over a year previously. The etiology was considered uncertain, although the postoperative bacteriologic observations might indicate a gonorrheal origin.

CASE 3.—A. J., aged 25, a white seaman, had had gonorrhea in 1920, and "syphilis" with a course of "five doses of arsphenamine" six months previous to the examination reported here. The patient had spent fifteen days at St. Vincents, Canary Islands, during the first part of October, 1926. He had observed, while there, a small ulcer appearing on the penis on the day following sexual intercourse. Seven days later, he noticed a swelling of the inguinal glands. He entered the U. S. Marine Hospital at Norfolk on November 13 with a soft and fluctuating bubo, which was opened on the fifteenth day. The mass drained pus, but continued to enlarge. It was removed on November 22.

The Wassermann reaction was negative. There was no evidence of venereal disease.

Histologically, an entire loss of normal structure was noted, with suppression of germinal centers and sinuses. There were large areas of loosely packed plasma cells with excentric, dense, round cartwheel nuclei and broad basophilic cytoplasm. Some of these possessed two or more nuclei. There were other areas of plasma cells mingled with fibroblasts and fibrous tissue. Foci of necrosis were present; some were filled with polymorphonuclear leukocytes and possessed only a narrow zone of fibroblasts at the margin, while others were older with broken down, amorphous contents and a broad zone of irregularly interlacing fibroblasts at the margin.

The foci of necrosis were of variable size and form. There were other areas in which the cells were mostly lymphocytes with a few hyperplastic reticulum cells. There were a few small areas of hemorrhage in the gland substance.

The capsule showed areas of infiltration with lymphocytes and plasma cells and of hemorrhage. One small gland showed lymphoid hyperplasia only.

CASE 4.—F. M., aged 26, white, an oiler and seaman, single, had had gonorrhea in 1924. He had never been in the tropics or in any ocean port. He had lived in Cleveland for four months prior to the examination reported here.

The present illness had begun during the course of frequent and promiscuous intercourse with negro prostitutes during the few months just prior to admission to the hospital. Pain and a slight swelling in the left inguinal region were first noticed on March 20, 1927. The patient entered the U. S. Marine Hospital at Cleveland on March 28. Physical examination disclosed nothing abnormal, except the moderately tender, firm swelling about the size of a walnut in the left inguinal region and a large, moderately tender, slightly indurated prostate. The prostatic secretion contained pus cells, but no gonococci. The urine showed pus, mucus and a small amount of albumin. The Wassermann reaction was negative. The blood picture on March 30 was: red cells, 5,150,000; hemoglobin, 75 per cent; white cells, 12,100; neutrophils, 79; lymphocytes, 11; large mononuclears, 2; transitionals, 7, and eosinophils, 1 per cent.

Under local treatment, the mass first subsided, then swelled and softened. Incision and drainage were done on April 8. Culture showed no growth and smears no organisms. The glands continued to be large and indurated, draining but little. Excision was done on April 18. After a brief febrile reaction, the temperature subsided to normal, and the wound granulated and healed. On May 2, the blood picture was: red cells, 4,050,000; hemoglobin, 80 per cent; white cells, 11,830; neutrophils, 60; lymphocytes, 24; large mononuclears, 10; transitionals, 4, and eosinophils, 2. Clinically, the condition corresponded to that in climatic bubo as described in Stitt's "Manual of Tropical Medicine."

Histologically, almost complete suppression of the normal structure was observed, germinal centers being recognized in only one node. There were small foci of necrosis with polymorphonuclear leukocytes in the centers and borders of irregularly disposed epithelioid cells. There were numerous small hemorrhages. Extensive areas of infiltration with plasma cells appeared, some of which possessed two or three nuclei. Small areas of coagulated edema were scattered through the gland substance. Areas of more or less dense fibrosis infiltrated with plasma cells were seen. The gland capsule showed extensive fibrosis of varying density, infiltrated with plasma cells, lymphocytes, plasmacytoid lymphocytes and histioid wandering cells, more especially in the less fibrotic areas. Young fibroblasts were numerous also. An area of hemorrhagic necrosis containing a few broken down cells and leukocytes was noted in the capsular tissue. Its margin showed partial fibrosis with lymphocytes and a few plasma cells and macrophages. Giant cells were absent. Several arterioles with organized thrombi infiltrated with lymphocytes were seen in the periglandular tissues.

CASE 5.—G. R., aged 29, a white seaman, about Feb. 11, 1927, noticed a small swelling in the left groin. This increased in size and became rather painful and tender. He entered the hospital on February 23. He offered no history of injury or of venereal disease. About January 11, he had had intercourse with a negro woman in Port Arthur, Texas. On admission, there was no evidence of venereal disease or of other local cause for lymphadenitis.

The clinical diagnosis was climatic bubo. Adenectomy was performed on February 24. The glands were enlarged, with necrotic centers and periglandular involvement.

Histologically, the lymph gland structure was largely obliterated, few germinal centers being preserved. There were numerous foci of necrosis bordered by narrow zones of swollen, ragged epithelioid cells with oxyphil cytoplasm. These foci contained cellular and nuclear débris. Many of them contained numerous polymorphonuclear leukocytes, and others swollen, vacuolated, degenerate, large mononuclear cells. There were a few small recent and older hemorrhages. There were extensive areas of infiltration of the lymphoid tissue with plasma cells. There were patches of proliferation of fibroblasts without collagen fibers. The capsule showed infiltration with lymphocytes and plasma cells.

CASE 6.—J. Z., aged 23, a white marine fireman, entered the hospital with a swelling of the left inguinal lymph glands of three weeks' duration. No lesion was found about the genitalia, anus or lower extremity to account for the lymphadenitis. The swelling had been gradual. The patient had just returned from South America and the West Indies.

The clinical diagnosis was climatic bubo. At operation on May 4, 1927, enlarged inguinal glands with central areas of necrosis were removed.

Histologically, there were multiple, irregularly shaped, small areas of necrosis with margins of epithelioid cells, some showing typical palisading, others being irregular. The contents were, in some, polymorphonuclear leukocytes, in some, leukocytes and lymphocytes; in others, amorphous products with a few nuclear fragments. There were also foci of epithelioid cells with or without central polymorphonuclear infiltration. Some parts of the gland showed diffuse interstitial fibrosis, infiltration by plasma cells and loss of normal structure with a few recent hemorrhages. Some of the plasma cells were multinuclear. One portion of the gland showed large, pale germinal centers with numerous mitotic figures and some small hemorrhages in the germinal centers.

CASE 7.—J. M., aged 32, a white seaman, for three months previous to the examination reported here, had been employed on a coastal fishing vessel. About four weeks previous, the glands in the left inguinal region began to enlarge. There was a gradual increase in size to a large, firm, tender mass measuring from 4 to 5 inches (from 10.16 to 12.7 cm.) in diameter. There was no history of venereal disease, though the patient had had intercourse with different women at intervals of from two to three weeks. Physical examination revealed only the local glandular mass, without evidence of venereal disease.

The red cells were 3,800,000; hemoglobin, 75 per cent and white cells 9,000. The differential count was not recorded. The Wassermann reaction was negative. The urine was essentially normal.

Adenectomy was done on June 8, 1927, about 11 a. m., and the material was received at the Hygienic Laboratory at 1:30 p. m. in a sterile container. Parts were at once fixed in Zenker Helly fluid. Part was used for cultures and for inoculations into animals, the results of which will be discussed later.

Histologically, only an occasional germinal center persisted. There were numerous focal lesions consisting of (a) small and larger interstitial hemorrhages, (b) small foci of necrosis with nuclear fragmentation in centers bordering direct on lymphoid tissue, (c) foci of epithelioid cells and large swollen mononuclear cells with oval leptochromatic nuclei, with or without a few polymorphonuclears in the center, and (d) areas of necrosis of irregular size and form, bordered by irregularly disposed or occasionally palisaded epithelioid cells, mingled with vacuolated macrophages and an occasional multinuclear Langhans' cell. The contents were broken-down cells and leukocytes.

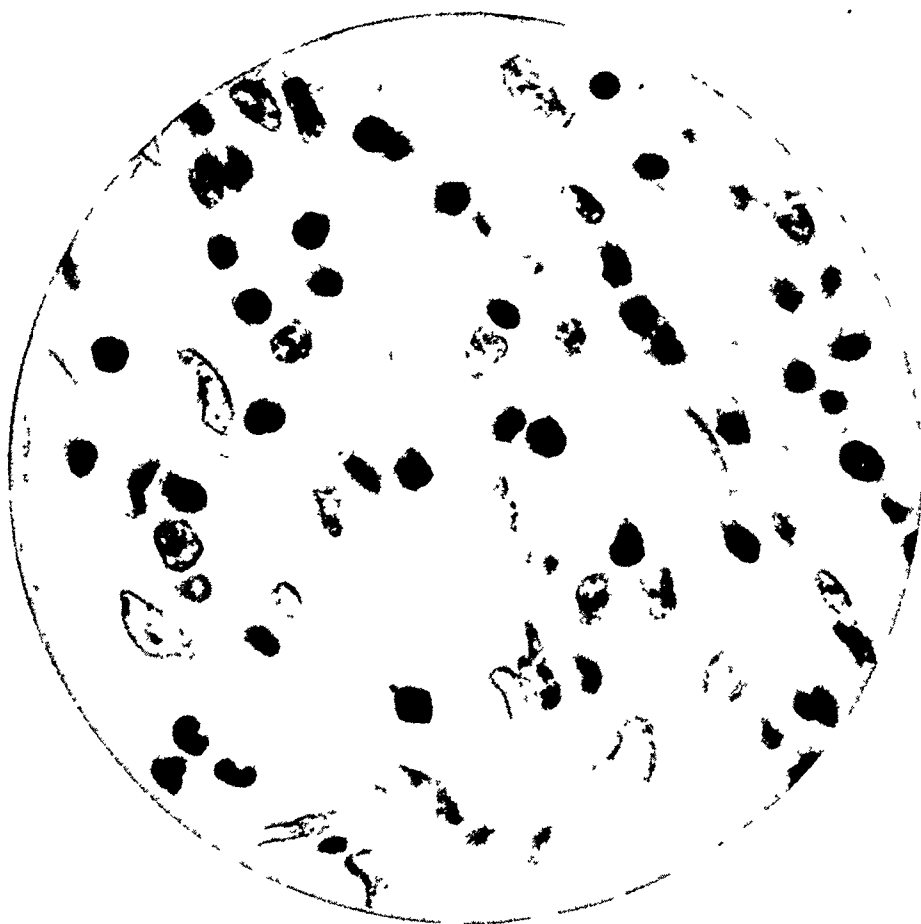


Fig. 2—Plasma cells and fibrosis in case 7: hematoxylin eosin. Zeiss 60X. 1.4 N. A Homal IV. 900 diameters, reduced in reproduction two-thirds.

Between these were areas in which plasma cells were mixed in varying proportions with the lymphocytes, from a few up to complete replacement. Some of these possessed from two to five nuclei of the characteristic cartwheel structure. These areas were often extensive. There were a few areas of proliferating fibroblasts with a few collagen fibers mixed with plasma cells, especially about arterioles.

The periglandular tissue showed patches of infiltration mainly with plasma cells. One small node showed only small active germinal centers, reticulo-endothelial hyperplasia with some degenerate, though not definitely necrotic cells of reticulum-macrophage type in the sinuses and a few small foci of infiltration with plasma cells in the pulp.



The cultures yielded an organism of the colon group, which could not be precisely identified with any of the hitherto described species. This organism was agglutinated by the patient's serum in a dilution of 1:80. Agglutination with serums of four other patients with climatic bubo was negative. Positive agglutinations in dilutions of 1:40 or over were obtained with five other serums of about 120 examined from patients suffering from various conditions. It was therefore concluded that the organism was not the specific cause of climatic bubo.

Inoculations of the fresh gland into rats, rabbits and guinea-pigs gave essentially negative results.

CASE 8.—J. G., aged 35, a sea cook, had been employed for six months prior to admission to the hospital on a Coast Guard cutter operating out of the port of New York. There had been no service in the tropics. On admission to the hospital, the patient presented a left inguinal lymphadenitis of one month's duration. There had been no genital lesion. Adenectomy was performed on Sept. 15, 1927, a fused mass of enlarged glands being found.

Histologically, there was complete loss of normal lymph gland structure, with foci of necrosis and smaller abscesses having irregular, reticulated margins, small recent and older hemorrhages, foci of edema and areas of infiltration with plasma cells, some of which possessed two or three nuclei, grading over into areas of proliferating fibroblasts mixed with plasma cells.

CASE 9.—F. M., aged 28, a negro seaman, on admission, presented a bilateral inguinal lymphadenitis of two months' duration for which no cause could be found and which was diagnosed climatic bubo clinically.

Adenectomy was done on July 16, 1928, a mass of partly necrotic glands being found on the right side, but no free pus.

Histologically, there were found, in two fragments, several rather large areas of caseous necrosis, and in all, multiple small foci of necrosis containing polymorphonuclear leukocytes and bordered by an irregular fringe of reticulo-endothelial cells, which were often swollen and degenerate. No germinal centers persisted in most of the tissue, and in the remainder, they were small and atrophic. There were considerable areas in which plasma cells and plasmacytoid lymphocytes predominated. Areas of fibrosis were present but were relatively inconspicuous. The capsule was densely fibrous with but few foci of infiltration with round cells.

CASE 10.—L. L., aged 23, a white seaman, on admission to the hospital presented an inguinal lymphadenitis of six weeks' duration. The affected gland had previously been incised. Cultures showed staphylococci. Clinically, the case appeared to be one of climatic bubo.

Histologically, there were abscesses of varying size, filled with polymorphonuclear leukocytes, bordered by a poorly defined fringe of epithelioid cells; areas of infiltration with plasma cells; areas of proliferation of fibroblasts and fibrosis; patches of reticulo-endothelial hyperplasia and patchy infiltration of the capsule with round cells.

CASE 11.—T. W., aged 21, a white seaman, on admission to the hospital presented an inguinal lymphadenitis of four weeks' duration. There were no lesions in the drainage area to account for the lymphadenitis. Clinically, the course of the disease was considered that of climatic bubo. At operation, the glands were enlarged and matted together.

Histologically, there was a lymphadenitis characterized by poorly walled off areas of necrosis containing cells with fragmented or karyolytic nuclei and usually polymorphonuclear leukocytes. The smaller foci of necrosis sometimes abutted directly on lymphoid tissue. The larger possessed an indefinite fringe of vacuolated, partially necrotic, stellate cells with large oval leptochromatic nuclei. The intervening gland pulp showed total disorganization of the normal structure, absence, in large part, of germinal centers, diffuse areas of proliferating fibroblasts with or without collagen fibers, inclosing between them many plasma cells and lymphocytes, and considerable areas packed with lymphocytes and a few hyper-



Fig. 3.—The margin of a focal lesion in case 12. Weigert fibrin. Technical details as in the legend for figure 2.

trophic reticulum cells. The capsule showed proliferation of fibroblasts, infiltration with lymphocytes and plasma cells, a few hemorrhages and some better delimited necrosis with borders of fibroblasts.

CASE 12.—T. J., aged 23, a negro seaman, said that he had been employed on a boat in Chesapeake Bay for the year previous to his admission to the hospital, and had not been farther south than Norfolk, Va. He stated that he had had no service in the tropics. He admitted frequent venereal exposure during this time, and the history given at the time of admission was that about two months previously he had noticed a slight swelling in both inguinal regions, that about

three weeks previously a sore had appeared on the "glands" and that after this the swelling in the inguinal region became more pronounced. The patient also stated that he had had a discharge for three weeks prior to admission, which was diagnosed as gonorrhea. He stated that he had had gonorrhea ten years before and a chancre in 1918, followed by antisyphilitic treatment. While the course of the adenitis and the macroscopic observations seemed to be consistent with climatic bubo, with the multiple venereal infection in this case the clinical diagnosis was rather uncertain. Clinically, however, the inguinal swelling was not the result of an infection with Ducrey's bacillus, as there was little tenderness

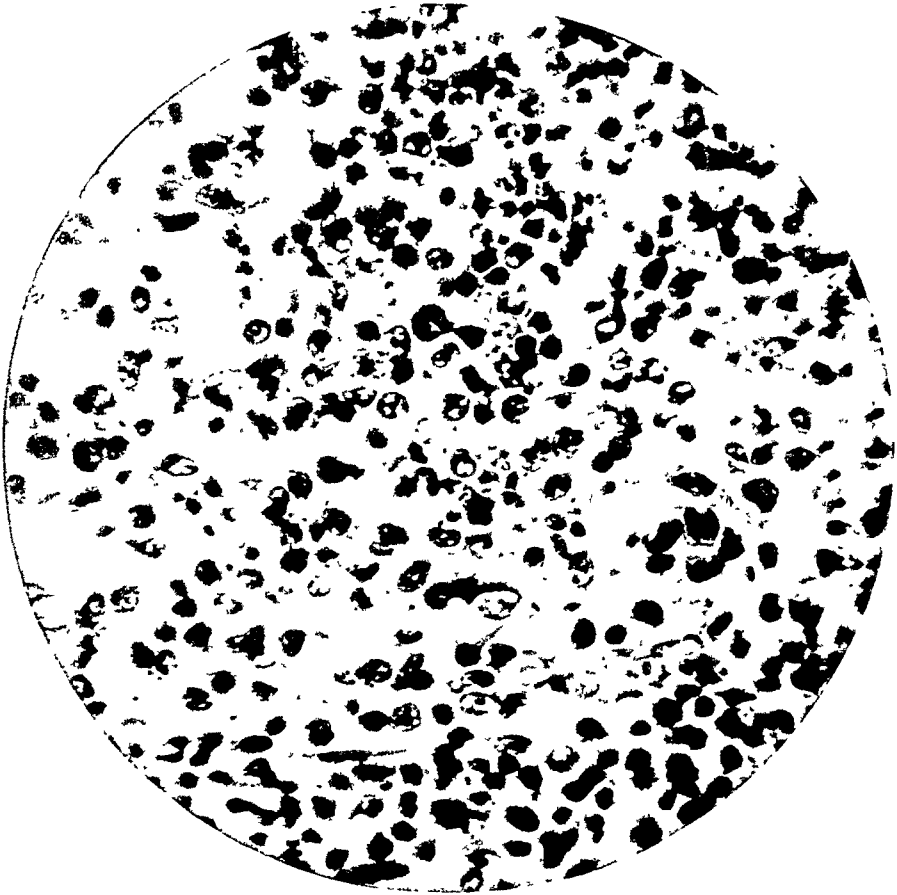


Fig. 4.—The margin of a focal lesion in case 13. Hematoxylin eosin. Zeiss 60X. 1.4 N. A. 7× Comp. oc. 500 diameters, reduced in reproduction two-thirds.

and little pain complained of at any time. Neither was it considered the result of a gonorrheal infection, as the condition was a subacute, rather painless adenopathy.

Microscopically, sections showed marked fibrosis of the periglandular tissues with patchy infiltration mainly with lymphocytes, a few plasma cells and macrophages and marked obliterative endarteritis.

In the gland tissue no germinal centers were seen. There was marked patchy interstitial fibrosis. Marked hyperplasia of the reticulo-endothelial tissue was noted in places. Some patches of recent hemorrhage and edema were seen. Multiple foci of necrosis containing pus cells, débris and coagulated serum and bordered by an irregular and rather indefinite fringe of degenerate epithelioid

cells were seen. Areas of infiltration with plasma cells, both in lymphoid tissue and in areas of proliferation of fibroblasts and fibrosis were seen. Some multinuclear plasma cells, containing two and three characteristic cartwheel nuclei, were found. Patches were seen in which there was a considerable quantity of yellowish-brown, granular pigment, free and in cells. One focal necrosis with practically no epithelioid border showed a large amount of fibrin among the pus cells and débris in the center.

CASE 13.—O. L., aged 26, a white seaman, said that he had just returned from Panama. He had signed on the SS. Feltore, which was bound for South American ports. He stated that when he arrived in Panama on the outward journey, he deserted the ship and remained in Panama approximately three weeks, coming back to Baltimore with the ship. Previous to this South American voyage he had not been going to sea. He stated that a few days after his arrival in Panama he noticed a swelling in the left groin. A few days later the right inguinal region began to swell. This swelling gradually grew worse. There was no history of any sore about the genitalia. He denied any previous venereal infection, except a soft chancre followed by inguinal adenitis in 1924. The patient admitted frequent exposure to venereal disease during his residence in Panama. There was no alleged injury as a possible causative factor. The clinical microscopic observations were consistent with climatic bubo. The only other sign of infection was carious teeth, a condition which is found in the majority of seamen.

Microscopically, sections showed a complete disorganization of the usual lymph gland structure, suppression of germinal centers, multiple irregular areas of fibrosis interspersed with and mixed with areas of infiltration with plasma cells. The latter pure areas contained often binuclear and trinuclear plasma cells, regularly numbers of plasmacytoid and ordinary lymphocytes, and often patches of hyperplastic reticulum cells. Among these types of tissue were areas of epithelioid cells centrally infiltrated with polymorphonuclears or surrounding abscesses filled with them, either well preserved or partly broken down so as to resemble caseous material. Little or no fibrin was demonstrable in the lesions.

Considerable areas of lymphocytes were also seen. There were numbers of small, fresh and older hemorrhages into the tissue.

CASE 14.—A. M., aged 40, a white seaman, had never served in the tropics. The last venereal exposure had occurred in Seattle, Wash., twenty days prior to the appearance of the lymphadenitis. After about six weeks, a mass of enlarged lymph glands with a few small foci of suppuration was removed from the right inguinal region. Recovery with firm healing was complete after a further six or seven weeks.

Histologically, one node showed simple lymphoid hyperplasia. The others showed loss of normal structure, suppression of germinal centers, areas of fibrosis and infiltration with plasma cells, areas of reticulo-endothelial proliferation and abscesses filled with polymorphonuclear leukocytes and broken down, large, round cells, and bordered by lymphoid tissue infiltrated with plasma cells. A few small hemorrhages were seen.

CASE 15.—W. H., aged 23, a white marine oiler, returned from a voyage to various ports on the east coast of South America and in the West Indies just prior to his entry into the Marine Hospital in Chelsea, Mass. The condition for which the complaint was made began on Oct. 25, 1928. The patient said that it

was brought on by heavy lifting, and that the swelling in the right groin appeared three days afterward, while he was in Buenos Aires. About the time of his admission to this hospital, on December 4, the gland broke down in two places, and pus was discharged through two sinuses, leading down to the interior of the gland. Adenectomy was done on December 11.

Histologically, sections of these lymph glands showed many small germinal centers made up of large, pale, leptochromatic cells with numerous mitotic figures and focal lesions consisting of patches of proliferated reticulum cells often centrally infiltrated with polymorphonuclear leukocytes, with or without necrosis of the reticulum cells. The margins of these areas were often infiltrated with large plasma cells with characteristic cartwheel nuclei, sometimes three or four in one cell. In other areas there was marked proliferation of the reticulo-endothelium of the sinuses, sometimes with deposition of a few collagen fibrils and a coincident infiltration with plasma cells. A few small recent hemorrhages were seen. The capsular tissue showed patchy infiltration with lymphocytes and plasma cells, often about thickened small vessels.

This case differed from some of the cases of climatic bubo in the persistence of the germinal centers, and in the relatively small amount of fibrosis and of infiltration with plasma cells. However, precisely similar focal lesions were seen in characteristic cases. Areas of infiltration with plasma cells and of hemorrhage were present and there was periadenitis.

CASE 16.—E. W., aged 20, a white seaman, presented a bilateral inguinal lymphadenitis of five weeks' duration. No venereal disease was demonstrable. The patient claimed to have strained himself lifting an iron beam.

Only one small node, 1 by 0.5 by 0.5 cm., was fixed for histologic study. This showed moderate proliferation of fibroblasts and an increase of interstitial fibrous tissue, some reticulo-endothelial thickening and suppression of the germinal centers. Foci of necrosis or other well defined focal lesions were lacking.

CASE 17.—H. H., aged 24, a white seaman, presented a lymphadenitis without any known or demonstrable etiologic factor. Development was slow. Adenectomy was performed two months after the onset. The glands were enlarged and necrotic, with marked periadenitis. Clinically and at operation, this was considered a case of climatic bubo.

Histologically, the glands were studded with fairly large abscesses the contents of which were partly homogenized basophilic material, partly polymorphonuclear leukocytes and fewer mononuclears. These abscesses were walled off by a somewhat irregular layer of cells resembling epithelioid cells, sometimes with definite palisading. Occasional small multinuclear giant cells occurred in this zone.

A few hyperplastic germinal centers were preserved. There were some areas of interstitial fibrosis infiltrated with lymphocytes or with plasma cells. The balance of the parenchyma of the gland was made up largely of lymphocytes, mingled with relatively few plasma cells, fairly numerous large lymphoblastic cells, a few phagocytic macrophages and hypertrophic reticulum cells.

CASE 18.—L. L., aged 28, a white marine fireman, for five months prior to admission to the hospital, had been sailing to Gulf or Mexican ports. He had just returned from Gulf ports. His last intercourse was about three months prior to admission, at Tampa, Fla. He denied any soreness or irritation following the intercourse. He said that he had not had venereal infection.

On March 25, while on duty on his ship, he was lifting a heavy object and noticed a sudden pain beginning in the heel and extending up the leg into the inguinal region. There was no wound on the foot. The pain was not severe, but was more like an electric shock. The pain continued in the inguinal region, and two days later he noticed that the glands were getting large. The swelling had grown progressively larger and more painful.

Clinically, the case was considered climatic bubo. At operation, the subinguinal group of glands were enlarged and matted together. Adenectomy was done on April 6.

Paraffin sections showed numerous small foci of necrosis, bounded by epithelioid or reticulum cells in some instances showing palisading. The centers were filled with polymorphonuclear leukocytes and nuclear fragments. Areas of edema were noted. A few lymph follicles were recognizable. Swelling of the endothelia of small vessels was prominent. Plasma cells were few.

There was a well marked periadenitis with edema and infiltration with plasma cells, hemorrhages, and, in one area, dense polymorphonuclear and hemorrhagic infiltration of the fatty tissue.

CASE 19.—A. E., aged 28, a white seaman, presented an inguinal lymphadenitis of four weeks' duration the onset of which occurred apparently without any predisposing factor. No primary lesion was found. At operation, an egg-size mass of fused lymph glands was removed.

Clinically, the case was one of climatic bubo. The patient's serum failed to agglutinate *Bacterium tularensis* or *B. abortus*.

Sections of the gland showed numerous focal abscesses filled with polymorphonuclear leukocytes and bordered by a usually irregular and narrow, but occasionally broad and palisaded, fringe of epithelioid cells. In the latter case, the central areas of necrosis were smaller and contained less pus. The capillaries and sinusoids showed well marked endothelial swelling. An occasional small hemorrhage was seen. There was no diffuse infiltration with plasma cells or fibrosis. Germinal centers were not recognized, but abscesses were frequent about the subcapsular zone where these are usually found.

CASE 20.—C. J., aged 23, a negro seaman, on admission to the hospital presented an inguinal lymphadenitis of one month's duration. No primary lesion was found. Cultures showed no growth and smears from the glands no bacteria. At operation, the enlarged glands were fused together.

Histologically, the lymph gland showed in some areas marked cordlike hypertrophy of the sinus endothelium, elsewhere hyperplasia of the germinal centers and elsewhere abscesses of varying sizes containing pus and cellular debris, bordered by irregularly interlaced, densely packed epithelioid cells. Nearby lymphoid tissue was infiltrated with polymorphonuclears and plasma cells. There were some patches of epithelioid cells without central necrosis.

The condition was diagnosed subacute suppurative lymphadenitis.

CASE 21.—M. L. C., aged 25, a white seaman, on admission to the hospital presented an inguinal lymphadenitis of five weeks' duration for which no primary cause could be found. A previous incision had been made, and staphylococci were cultivated from the glands. At operation, the enlarged glands were fused together. Both grossly and clinically, the case appeared to be one of climatic bubo.

Sections showed numerous irregularly shaped foci of necrosis filled with leukocytes and necrotic debris, bordered by definitely palisaded epithelioid cells, among

which no giant cells were noted. Some metaplasia of the plasma cells of the surrounding lymphoid tissue was noted. Germinal centers were lacking. There was moderate patchy infiltration of the capsule with round cells.

The patient's serum did not agglutinate with *B. tularensis*.

CASE 22.—E. S., aged 20, a white boatswain, on admission, presented an enlarged right inguinal gland of some three or four weeks' duration. The patient had had gonorrhea and chancre in 1925. Adenectomy was done on April 18, 1927.

Histologically, this lymphadenitis was characterized by partial loss of the normal structure of the gland, relatively few germinal centers persisting; by areas of recent hemorrhage and of edema; by well marked swelling of the endothelia of the smaller vessels and of the reticulo-endothelial cells of the sinuses; by an occasional small polymorphonuclear-filled abscess bordered by large cells with relatively pale vesicular nuclei, and by a well marked extensive periadenitis with swollen endothelia, dense infiltration with lymphocytes and plasma cells and an occasional fairly well formed multinuclear giant cell with peripheral nuclei.

The abscesses contained, besides polymorphonuclear leukocytes, nuclear fragments and large mononuclear cells of the macrophage type. The bulk of the tissue of the gland was made up of lymphocytes, intermingled with an occasional eosinophil and a moderate number of plasma cells. In a few foci these last predominated. Only an occasional small area of fibrosis was present.

CASE 23.—R. W. G., a white marine, was seen in the U. S. Naval Hospital in Washington under the care of Dr. White of the Naval Medical Corps, to whom I am indebted for the data and material.

Clinically, the case was one of climatic bubo. The onset occurred about June 15. At operation, August 10, the glands were apparently entirely broken down. Cultures yielded a staphylococcus and a diphtheroid, which were not further studied.

Histologically, no lymph gland tissue remained. The specimen consisted of fibrous tissue and inflammatory granulation tissue, in which were numerous plasma cells, large vacuolated macrophages, islets of lymphocytes and occasional giant cells with many peripheral nuclei. There were no definite tubercles and acid-fast bacilli were not found on extensive search.

CASE 24.—D. McP., aged 27, a white seaman, on April 25, 1927, was struck in the left groin. Acute lymphadenitis resulted, which was considered a climatic bubo. Partial adenectomy was performed shortly thereafter at Port Said, Egypt. The remaining lymph nodes became tender at intervals. Adenectomy was done on March 23, 1928. The histologic material consisted of a node measuring 1 by 0.5 inches (2.5 by 1.27 cm.).

Part of the gland showed a simple lymphoid hyperplasia of rather pronounced grade with concomitant interstitial fibrosis. The remainder showed a number of irregularly shaped caseous areas each surrounded by a wall of fibrous tissue of remarkably even thickness and suggesting strongly in the arrangement of its fiber an earlier palisading of epithelioid cells. Some of the features of these lesions suggested a late healed and inspissated suppurative lymphadenitis.

The agglutination with *B. tularensis* was negative.

CASE 25.—C. J., aged 26, a white seaman, presented a climatic or tropical bubo of fourteen weeks' duration. Aerobic and anaerobic cultures showed no growth. The histologic material consisted of an inguinal lymph node 0.75 by 0.5 inches (1.87 by 1.27 cm.), with a central area of suppuration.

Histologically, the germinal centers were small, but of loose texture and made up of large, pale staining cells of the lymphoblast type. The fibrous trabeculae of the gland were generally prominent and thickened. A few small fibrosing scars containing a few plasma cells were seen. There were several small irregular abscesses with largely necrotic contents of broken down polymorphonuclear leukocytes. The walls were partly of the palisaded epithelioid cell type, partly fibrosing.

CASE 26.—A. S., aged 28, a white seaman, presented an inguinal lymphadenitis of four weeks' duration for which no primary lesion could be found. The clinical course was considered that of climatic bubo. At operation, the glands were fused together, showing necrotic centers.

Sections showed in two glands several abscesses containing partially broken-down and homogenized pus bordered by a narrow layer of fibroblasts and often considerable fibrous tissue outside these. One gland showed marked proliferation of fibroblasts and infiltration with plasma cells with recent hemorrhage in its capsule. Another showed considerable interstitial fibrosis. All but this last showed large, pale, active germinal centers and hypertrophy of the reticulo-endothelial tissue. Obliterative endarteritis was seen in inflamed areas of the capsule.

CASE 27.—J. G., aged 24, a white seaman, presented an inguinal lymphadenitis of two months' duration on which a clinical diagnosis of climatic bubo was made. At operation, a mass of inguinal glands 2.5 to 1.25 inches (6.2 by 3.1 cm.) was found. These were fused together and showed necrotic centers, but no free pus.

Histologically, this lymphadenitis showed scattered small abscesses filled with polymorphonuclear leukocytes poorly walled off and with little necrosis. There were diffuse and marked reticulo-endothelial hyperplasia, considerable interstitial fibrosis, suppression of germinal centers and capsular changes consisting of patchy infiltration with lymphocytes and polymorphonuclears and fibroblastic proliferation in the fatty tissue.

CASE 28.—L. T., aged 25, a white boatswain, had had gonorrhea six months previous to his admission to the hospital. About three weeks before entering the hospital, he was on the West Coast of Africa. Three days before admission, swelling and tenderness appeared in the left inguinal region. There was no preceding injury, and information as to venereal exposures was not obtained. Evidence of coincident venereal disease was lacking.

Histologically, there were multiple foci of necrosis bordered by irregularly disposed, partly rounded up reticulum cells, filled with leukocytes, swollen vacuolated macrophages and lymphocytes, all in varying stages of necrosis. There were also areas of proliferation of reticulo-endothelial cells. These areas sometimes showed central infiltration with polymorphonuclears. Aside from these, there was a large measure of suppression of sinus structure and germinal centers. In place of these there were areas of infiltration with plasma cells and lymphocytes and proliferation of fibroblasts with relatively little fibrosis. The gland capsule was fibrous and well defined, with a few areas of infiltration with plasma cells. A small part of the tissue showed well marked reticulo-endothelial hyperplasia and enlarged, pale germinal centers with numerous mitotic figures.

CASE 29.—I. F., aged 30, a white marine fireman, had never seen service in the tropics, having sailed only along the New England coast. He said that he had not had venereal diseases or been exposed to them. There was no antecedent injury. On admission, he presented a painful swelling in the right groin of one month's duration. Evidence of venereal disease and of local injury was lacking.



Histologically, there were extensive areas of sheetlike hyperplasia of reticulo-endothelial cells. These areas often showed central infiltration with polymorphonuclears or more or less extensive formation of abscesses. The abscesses contained principally polymorphonuclear leukocytes and a few vacuolated macrophages. Between these were more or less extensive areas of infiltration with lymphocytes and of plasma cells, often with a concomitant interstitial proliferation of fibroblasts and fibrosis. A few germinal centers persisted, showing numerous mitoses, and there were adjoining areas of reticulo-endothelial hyperplasia. Some of the abscesses were seen partly invading germinal centers. The capsule showed marked patchy infiltration with plasma cells and thickening and fibrosis of small vessels.

#### COMMENT AND SUMMARY

Histologically, these cases fall into two groups, one comprising cases 1 to 15 and 28 and 29, cases which correspond well with those described by Letulle and Nattan-Larrier, Müller and Justi, Castellani and Chalmers, and by Uribe, and the other comprising cases 16 to 27, which present no especial characteristics to differentiate them from cases of ordinary lymphadenitis.

Summarizing, the first group showed primarily foci of reticulo-endothelial proliferation with central nuclear fragmentation and necrosis, central infiltration with polymorphonuclears or definite formation of abscesses and later homogenization of the contents. In addition, small hemorrhages were frequent. Capillary thickening was common. Often the germinal centers and lymph sinuses were obliterated. Perhaps the most characteristic feature was the occurrence of considerable areas of dense infiltration with plasma cells, pure, or mixed with proliferating fibroblasts and areas of fibrosis. Regularly also there was well marked periadenitis with infiltration with plasma cells, vascular thickening and fibrosis.

Neither bacteria nor cell inclusions from the nuclear debris in the focal lesions in any of the cases of this group could be identified with certainty.

When these two histologic groups were considered in regard to certain etiologic factors, it was found that injuries were the alleged cause in two cases in one group and in three in the other. Seven of the histologically characteristic group and three of the other group had served in the tropics, while six of the first and none of the second group had not. Data as to service in the tropics were not available in thirteen cases, four in the first and nine in the second group. A possible venereal origin in the sense that the venereal contacts had preceded the origin of the bubo, not in the sense that the venereal diseases coexisted with it, was indicated in seven cases, all in the first histologic group. Trauma was not alleged and data as to possible venereal origin were not obtained in eight cases of the first group and in nine cases of the second, noncharacteristic group.

It should be here noted that the first group includes certain cases in which the clinical diagnosis of climatic bubo was not made until after the suggestion was made by the pathologist, while the second group naturally includes only cases clinically so diagnosed.

TABLE 1.—*The Relation of Service in the Tropics to the Two Histologic Groups of Cases of Inguinal Lymphadenitis*

Data on Service	Characteristic Histologically Group	Heterogenous Histologically Group	Total
Definite history of recent service.....	7	3	10
No service in tropics.....	6	0	6
No data as to service in tropics.....	4	9	13
Total .....	17	12	29

TABLE 2.—*The Relation of Certain Other Factors to the Two Histologic Groups of Cases of Inguinal Lymphadenitis*

Other Factors	Characteristic Histologically Group	Heterogenous Histologically Group	Total
Injury alleged as cause.....	2	3	5
Venereal exposure preceding and possibly causative of the illness.....	7	0	7
No history of injury and no data as to venereal contacts .....	8	9	17
Total .....	17	12	29

#### CONCLUSIONS

Climatic bubo is not a clinicopathologic entity. About half the cases here described were characteristic histologically and consistent with one another and with the published descriptions (1, 2, 4, 14, 15) of certain authors. The remaining cases were of the ordinary, nonspecific varieties of suppurative lymphadenitis.

Climatic bubo, while probably commoner in the tropics, is not restricted to this geographic area.

# A CASE OF RHINOSPORIDIUM SEEBERI IN A RESIDENT OF THE UNITED STATES \*

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AND

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CHICAGO

On Oct. 24, 1928, we received from Dr. M. C. Van de Venter, of Keokuk, Iowa, a tissue for histologic examination, marked "tumor of the anterior superior portion of the nasal septum."

Microscopic examination showed the tissue to be infected with *Rhinosporidium seeberi*. This organism was unfamiliar to us, but the diagnosis was suggested by Dr. Vida A. Latham and later confirmed by Prof. H. B. Ward, of the University of Illinois.

This parasite was first reported in 1900 by Seeber<sup>1</sup> from Buenos Aires. His patient had a large nasal polypus, which was removed with a snare, and much bleeding followed the operation. He described the parasites, which were numerous in the connective tissue of the tumor. This patient was a native of Italy, but had lived in the Argentine Republic since the age of 3 years.

In 1903, O'Kinealy<sup>2</sup> showed at a meeting of the Laryngological Society of London a section of a nasal polyp which had been removed in Calcutta from a native of India. Minchin and Fantham<sup>3</sup> studied this material and described the parasite in 1905, naming it *Rhinosporidium kinealyi*.

A number of other cases have been reported from India and from Ceylon by various observers. In fact, Wright<sup>4</sup> stated that this nasal infection is not uncommon in Madras.

The greater number of the rhinosporidial growths reported have been from the nasal cavity, but the parasite has been found in polypoid

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\* Submitted for publication, Feb. 6, 1929.

\* From the Lincoln-Gardner Laboratory.

1. Seeber, G. R.: Un nuevo esporozoario parásito del hombre dos casos encontrados en pólipos nasales, Thesis, Univ. Nac. de Buenos Aires, 1900.

2. O'Kinealy, F.: Localized Psorospermiosis of the Mucous Membrane of the Septum Nasi, Proc. Laryngol. Soc. London **10**:109, 1903.

3. Minchin, E. A., and Fantham, H. B.: Rhinosporidium Kinealyi, n. g., a New Sporozoon from the Mucous Membrane of the Septum Nasi of Man, Quart. J. Micr. Sc. **49**:521, 1905.

4. Wright, J.: A Nasal Sporozoon Rhinosporidium Kinealyi, New York M. J. **86**:1149, 1907.

outgrowths of the nasopharynx, the uvula, the conjunctiva, the ear and the penis. The parasite has not been found outside the human body.

Only one case has been reported from the United States. In 1907, Wright<sup>4</sup> found rhinosporidium in a nasal tumor from a man who had lived his whole life near Memphis, Tenn.

Ashworth<sup>5</sup> between 1917 and 1921 had the unusual opportunity of studying this parasite in material from an Indian medical student, who was under observation during most of that time and who had several



Fig. 1.—A portion of a ripe sporangium showing undeveloped spores at the periphery and ripe ones nearer the center. The ripe spores contain deeply staining spherules;  $\times 1,000$ .

operations on account of the recurrence of nasal polypi. Ashworth studied the life history and development of *Rhinosporidium seeberi* in all its stages, and his account published in the "Transactions of the Royal Society of Edinburgh" in 1923 is a classic. He placed this organism under the *Phycomycetes* of the suborder *Chytridineae*, which

5. Ashworth, J. H.: On *Rhinosporidium Seeberi* (Wernicke, 1903), with Special Reference to Its Sporulation and Affinities, Tr. Roy. Soc. Edinburgh, 1920-1921, vol. 53, pt. 2, no. 16. Issued separately March 20, 1923.

have no mycelium. He left the exact classification undetermined, since it is unknown whether the spores develop outside the human body.

We are indebted to Prof. W. H. Taliaferro, of the University of Chicago, for the opportunity of studying some of Ashworth's slides; also for suggestions about staining and preparing our own material.

#### REPORT OF CASE

The history of the case in question, the tissue from which was supplied to us by Dr. M. C. Van de Venter, who removed the nasal tumor, is as follows.

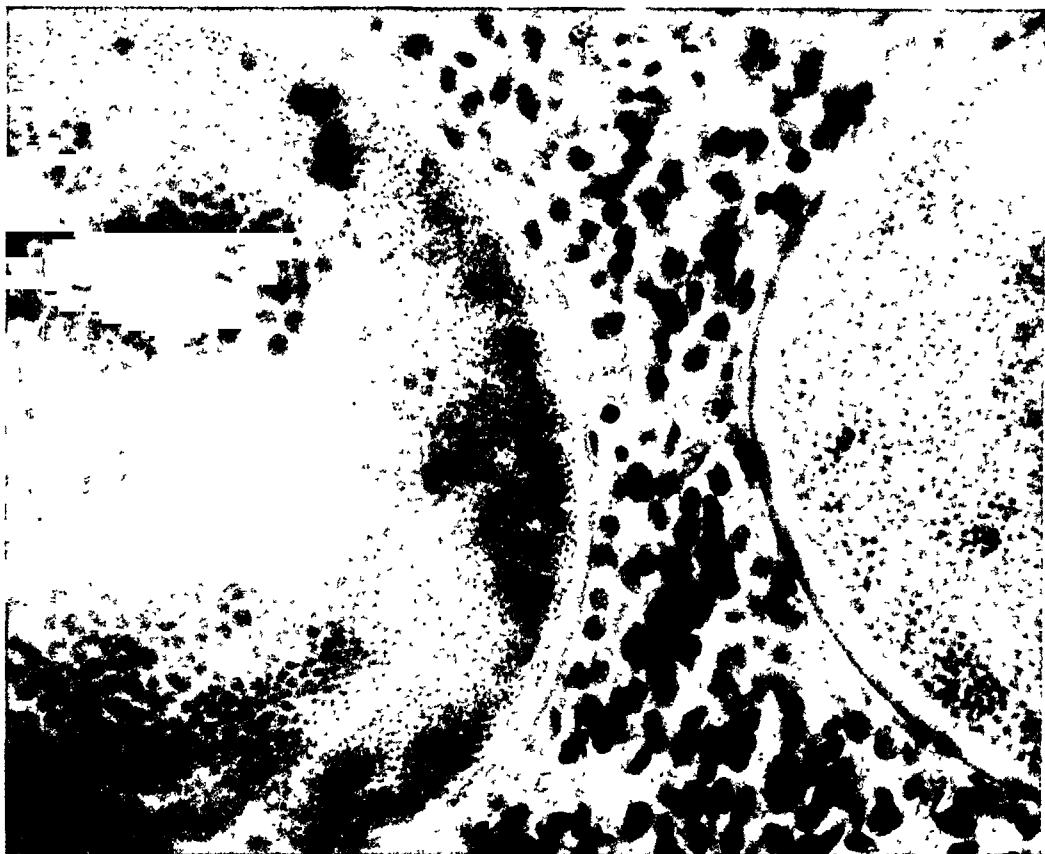


Fig. 2.—Portions of unripe and ripe sporangia;  $\times 470$ .

A man, aged 40, was born in Carthage, Ill., and had lived there until he was about 17, when he spent three years in Chicago. At some later time, he lived one year in Oklahoma. In 1925, he spent nine months in Florida. He had never been outside the United States.

Thirty years before he came to Dr. Van de Venter, an operation was performed on the nose, and at that time the septum was perforated. The patient had no further trouble with the nose until twenty-two years later. Then he commenced to have a discharge and occasional bleeding.

About Oct. 20, 1928, Dr. Van de Venter removed the tumor which is described in the present paper. He stated that the patient was in good general health, that his blood gave a negative Wassermann reaction, and that healing was rapid after

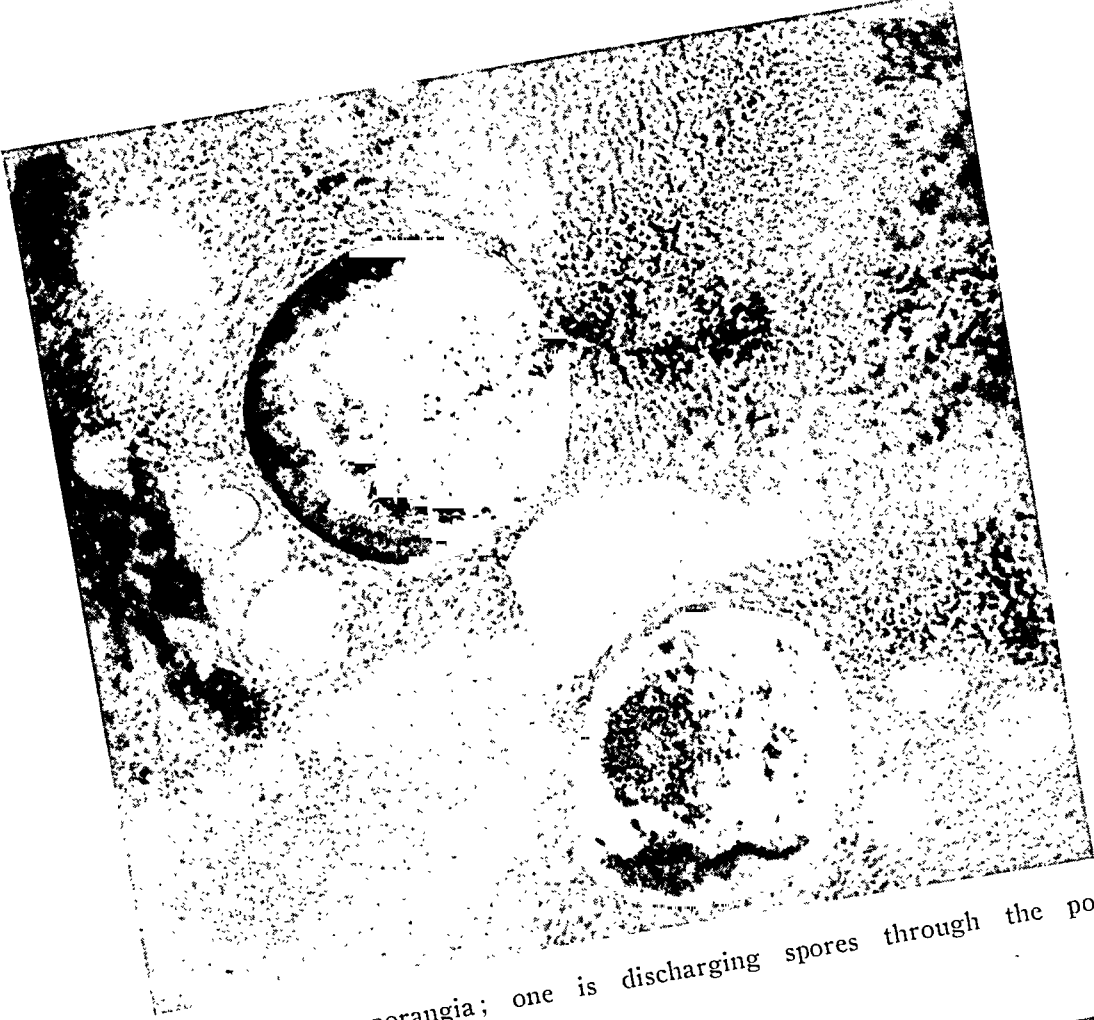


Fig. 3.—Ripe sporangia; one is discharging spores through the pore;  
 × 125.

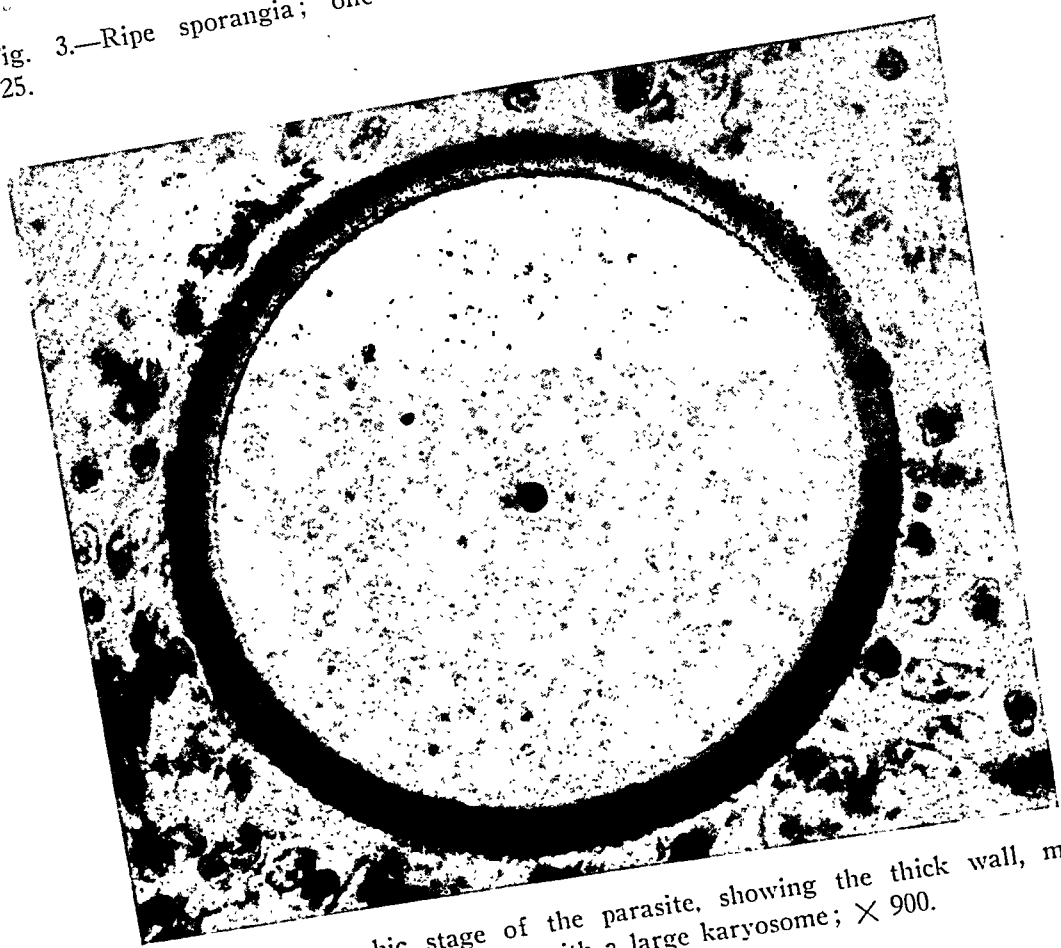


Fig. 4.—The trophic stage of the parasite, showing the thick wall, many  
 nutrient granules and one nucleus with a large karyosome; × 900.

the operation. The patient was seen about six weeks after the operation, and there was no sign of recurrence.

The tumor when received by us was in formaldehyde. Its gross appearance was that of an ordinary nasal polypus about 1 cm. in diameter. We embedded it in celloidin and used Delafield's hematoxylin for staining. Later, in the study of cell division and nuclear structure, we used Heidenhain's iron hematoxylin.

The sections showed an inflammatory polypus rich in cell elements, such as lymphocytes, leukocytes, plasma cells and large mononucleated epithelial cells. Dipping into the polypus were many invaginations of the surface epithelium, some of which in the sections had the appearance of cysts. These pseudocysts were lined with columnar and cuboidal cells, while the surface epithelium was largely squamous, but in some areas was columnar and cuboidal. A striking feature of the histologic picture was the infiltration of the tissue by numerous polymorphonuclear leukocytes permeating the exudate of mucus, spores and blood, which often filled the pseudocysts and spread over the surface of the tumor. Venous sinuses were present and the numerous blood vessels were congested. There was also hemorrhage as shown by many red blood cells outside the blood vessels.

The most striking feature was the parasite, seen in all stages of development, the trophic stages, the sporangia and the spores. The trophic stages, which in appearance, were thick-walled spheres varying in size from 6 to 60 microns in diameter, developed from the spores, and through nuclear division grew into the sporangia. The sporangia, like the trophic stages, were spherical, but were less perfect in outline, and much larger, up to 300 microns in diameter, and had a thinner wall with a pore opening. They contained hundreds of spores and, when mature, discharged them through the pore into the surrounding tissue, or on the surface, depending on their location. The freed spores that were capable of development grew into the trophic stages, and the cycle continued.

In the ripe sporangium (figs. 1 and 2), the spores varied in appearance: those at the periphery looked like pale, uniformly staining globules about 3 microns in diameter, while those toward the center were from 7 to 9 microns in diameter, their cytoplasm being vacuolated and containing from 2 to 16 spherules. These spherules were so prominent and stained so deeply that the nucleus of the spore could hardly be seen. Earlier writers thought the spherules were reproductive sporules, but Ashworth determined that they were proteinaceous bodies and not nuclear. During the development of the young spores into the fully formed ones, the sporangium grew considerably in size, and was then the largest stage of the parasite seen in the tumor. In most of the sporangia, only a small proportion of the spores formed, and continued development to the ripe stage. Ultimately, the sporangium burst and its ripe and undeveloped spores embedded in mucus were discharged into the surrounding tissue or on the surface of the tumor to be passed in the nasal secretion (fig. 3). The compact mass of spores within the sporangium spread over a much larger area when released from the confining wall of the sporangium, so that one saw in the polypus large masses of spores embedded in mucus and intermingled with polymorphonuclear leukocytes, as well as numerous individual spores scattered among the tissue cells. Some of the pseudocysts were filled with this mixture of spores, sporules from broken-down spores, mucus and leukocytes, and often showed the collapsed sporangium wall.

The fully formed spores in the tissue after their escape from the sporangium lost their spherules, developed a thick wall and became transformed into the trophic stage. This showed a single, spherical nearly centric nucleus, with a distinct envelope and a deeply staining spherical karyosome. Its cytoplasm contained numerous granules of nutrient material, which increased in number and

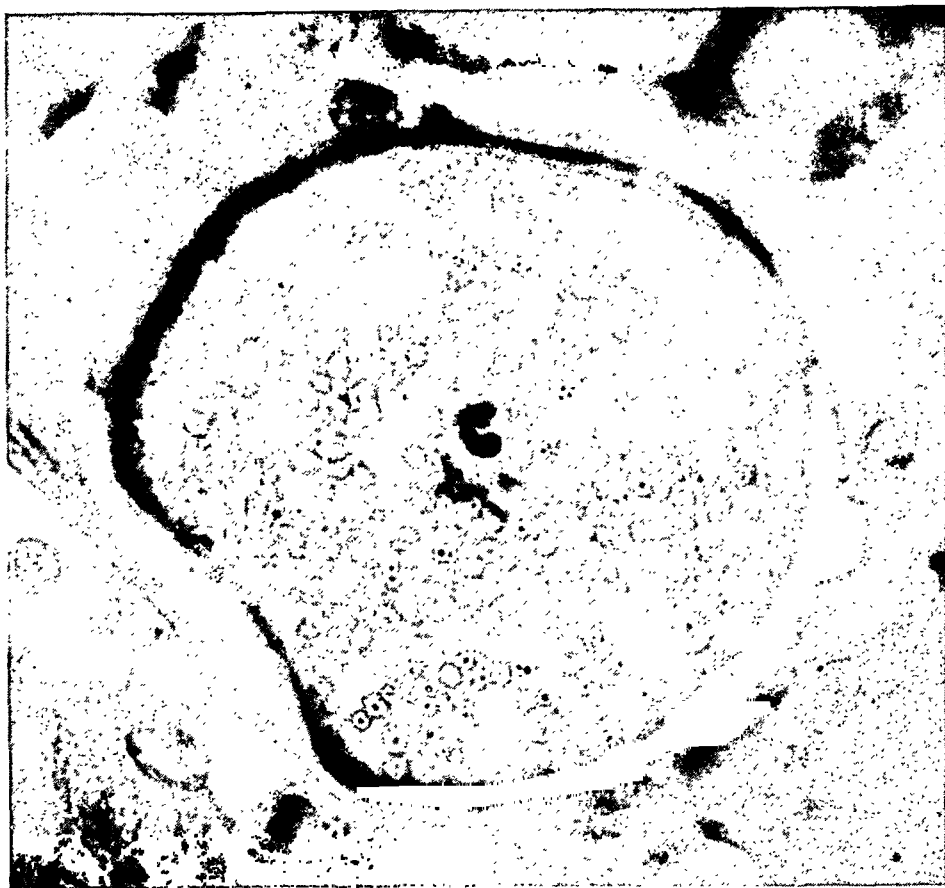


Fig. 5.—The trophic form of the parasite, showing nuclear changes preparatory to the first division;  $\times 1,500$ .

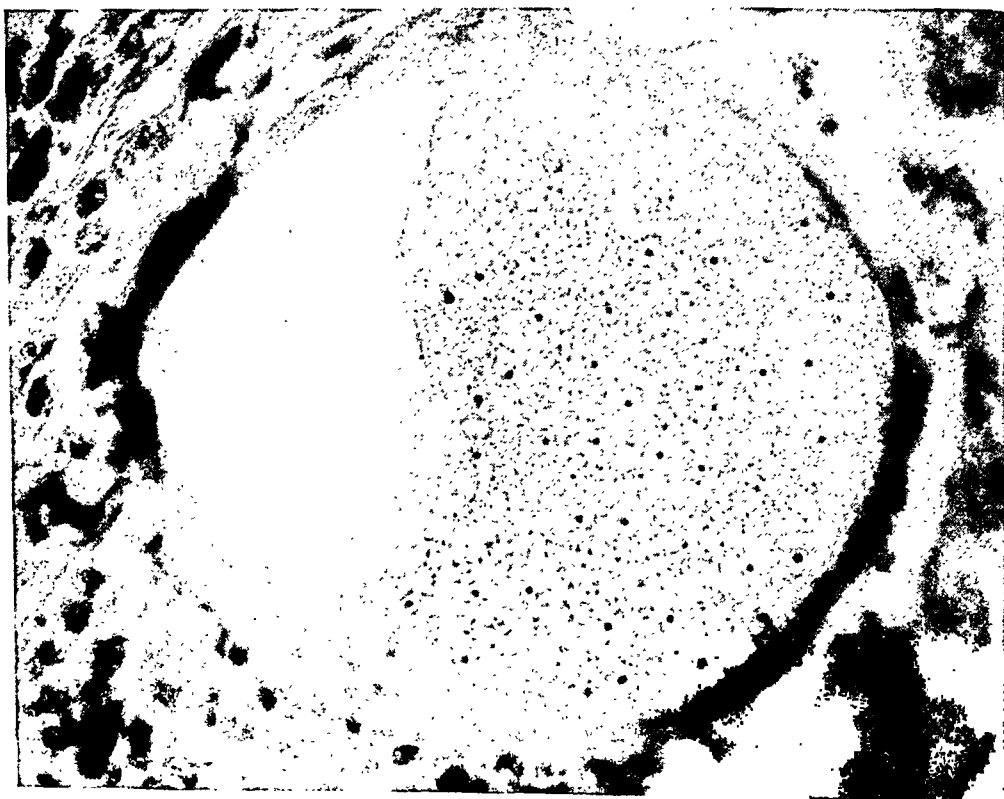


Fig. 6.—The parasite, showing many nuclei, in the resting stage;  $\times 650$ .



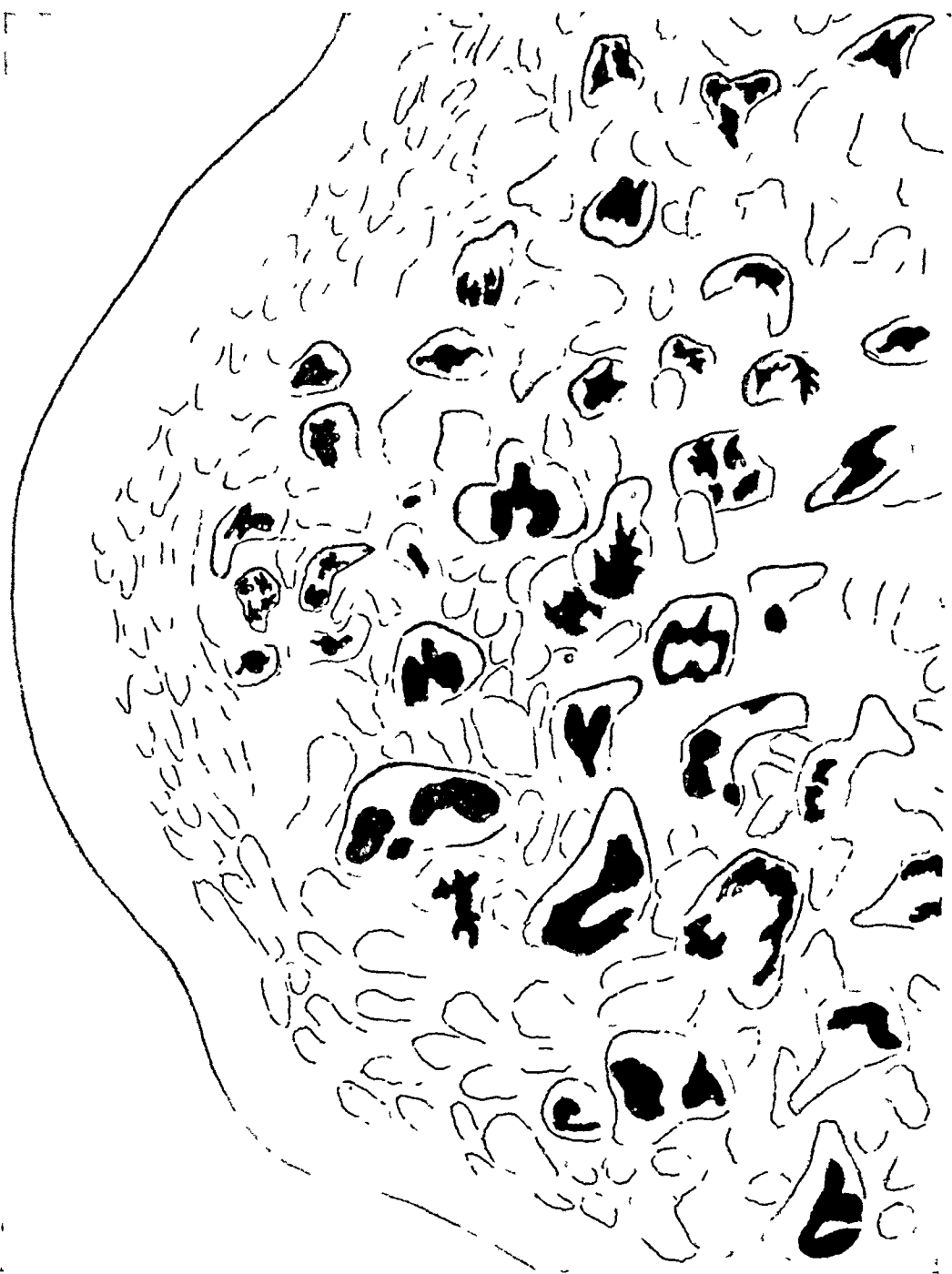


Fig 7.—A portion of a sporangium, showing one of the latest nuclear divisions, after division of the cytoplasm (from a drawing).

size with the growth of the parasite (fig. 4). We found parasites in this stage very numerous in the tumor, but examples of parasites undergoing nuclear division were found only after considerable search.

Nuclear division began when the parasite was from about 40 to 45 microns in diameter. Ashworth in his monograph described in detail twelve nuclear divisions, which resulted in about 16,000 spores. We were unable to demonstrate in our sections the early nuclear mitoses, but found the changes in the nucleus preparatory to its division (fig. 5). Our sections also showed the stage in which many minute nuclei are in the resting condition with the cytoplasm not yet divided into cells (fig. 6).

Figure 7 shows one of the late nuclear divisions, after the contents were divided into spores. Many of these nuclei were in the dividing state. The next stage seen in our material was the sporangium with well differentiated young spores, and finally the ripe sporangium with mature spores (fig. 2).

We are reporting this case because of its rarity. So far as we have been able to find, this is the second case of *Rhinosporidium Seeberi* reported in the United States.

# PRIMARY CARCINOMA OF THE LUNGS

## III. HISTOGENESIS AND METAPLASIA OF BRONCHIAL EPITHELIUM\*

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Until recent times, the lungs were considered to contain epithelial cells connected with three different structures: (1) the epithelium lining the bronchi; (2) the epithelial cells which form the mucous glands, and (3) the epithelium lining the pulmonary alveoli (the air sacs). Histogenetically, therefore, primary cancer of the lung was classified into three groups according to the epithelial units mentioned. Microscopically, the classification was based on the following criteria: (1) on the type of cells which were said to resemble those of the matrix, and (2) on their arrangement. Some observers have also based their genetic discrimination on the gross appearance of the tumor. Ewing,<sup>1</sup> who classified the tumor into the groups mentioned, stated that the combination of the clinical history, gross anatomy and histologic structure will furnish a "reasonably certain and acceptable histogenic classification." This, however, cannot be relied on. Those who have studied primary pulmonary cancer are familiar with the almost kaleidoscopic clinical manifestations of this malignant disease. The gross anatomy in this condition, as in cancer of other organs, will rarely furnish irrefutable criteria as to the particular histologic structure which gave origin to the growth. Finally, the microscopic features of a fully developed pulmonary tumor will point to its histogenesis in exceptional cases only; the morphology of the neoplastic cells varies from one tumor to another (columnar, cuboidal, spindle-shaped, so-called "oat" cells, squamous epithelial cells, basal cells), and even in the same tumor their form frequently varies from area to area. On the contrary the arrangement of the cells is rather uniform, in most instances being that of adenocarcinoma (fig. 1).

The difficulties in the genetic tracing of a primary pulmonary cancer can be illustrated by the fact that most observers are critical as to the existence of tumors having their origin in the alveolar cell, while others

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\* Submitted for publication, March 15, 1929.

\* From the Surgical Department of the Peter Bent Brigham Hospital.

\* The preceding papers of this series have been: Primary Carcinoma of the Lungs, *Arch. Int. Med.* **35**:1 (Jan.) 1925; Primary Carcinoma of the Lungs: Further Study, with Particular Attention to Incidence, Diagnosis and Metastases to the Central Nervous System, *ibid.* **40**:340 (Sept.) 1927.

1. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 851.

(Letulle<sup>2</sup>) do not include tumors originating in the mucous glands in their classification.

Of particular interest are blastomas said to originate from the cells lining the pulmonary alveoli (so-called respiratory epithelium).

#### CANCER ORIGINATING FROM CELLS LINING THE ALVEOLAR WALL

Pässler<sup>3</sup> (1896) was the first to give a comprehensive discussion of the question and also to review fifty-four cases of primary cancer



Fig. 1.—Primary bronchiogenic cancer, infiltrating type. The lung is contracted and firm. On cut surface, it resembles a pneumonic lung in the stage of red hepatisation. The histologic structure of the tumor is shown in figure 3.

of the lung which he found at that period in the literature. He reached the conclusion that of this number forty-seven originated, in all

2. Letulle, M.: *Le poumon*, Paris, Maloine, 1924.

3. Pässler, H.: *Ueber das primäre Carcinom der Lunge*, Virchows Arch. f. path. Anat. **145**:191, 1896.

probability, in the bronchial mucosa; while in the others, the histogenesis could not be established. He stated, moreover, that cancers having their origin in the pulmonary parenchyma are unknown, or at least that the nonparticipation of the bronchial epithelium in these cases could not be excluded. Dömeny<sup>4</sup> (1902) thought that tumors made up of small and large nodules composed of small polymorphic cells forming "pearls" are of alveolar origin. Other pathologists claimed, that squamous epithelial tumors usually originate in the alveolar cells (Beitzke<sup>5</sup>).

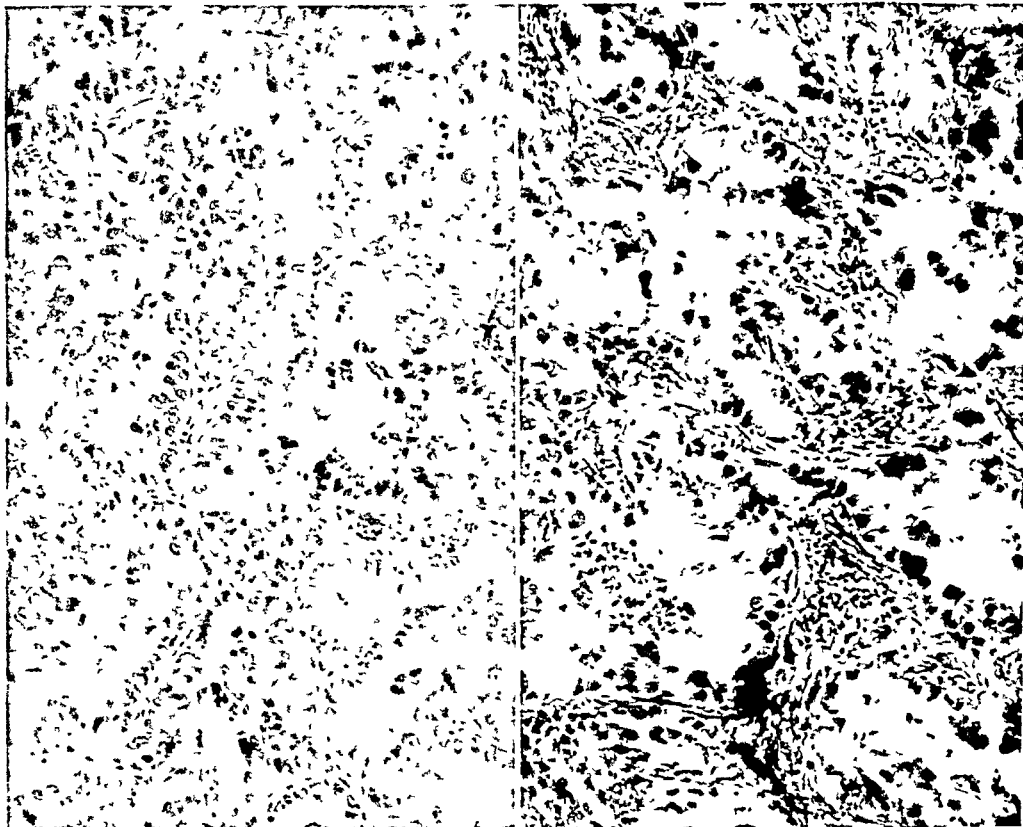


Figure 2

Fig 2.—Primary bronchiogenic cancer. Tumor lining the wall of the alveoli.

Figure 3

Fig. 3.—Primary bronchiogenic cancer. The thickened alveolar wall forms papillary projections lined by neoplastic cells. The whole lung shows a marked sclerosis. The gross appearance of the lung is given in figure 1.

In 1912, Adler<sup>6</sup> published his monograph containing a critical review of 374 cases of primary carcinoma of the lungs. He wrote:

4. Dömeny, P : Zur Kenntniss des Lungencarcinoms, *Ztschr. f. Heilk.* **23**: 407, 1902.

5. Beitzke, H.: *Atmungsorgane*, in Aschoff: *Pathologische Anatomie*, Jena, G. Fischer, 1923, vol. 2, p. 255.

6. Adler, T : *Primary Malignant Growths of the Lungs and Bronchi*, New York, Paul B Hoeber, 1912.

"It is now held that carcinoma starting from the pulmonary alveoli is extremely rare, and some go so far as to deny its existence altogether." Adler himself was of the opinion that the great majority of primary carcinomas of the lungs develop from the bronchi, and that a cancer of the lung is, strictly speaking, a bronchial carcinoma. Nevertheless, he admitted the existence of alveolar cell tumors which are built up "not of flat but of cylindrical epithelium."

My own studies in this matter have convinced me that the cells lining the air sacs do not give rise to carcinoma. Clinical and pathologic observations have led me to the conclusion<sup>7</sup> that these cells are not epithelial but mesenchymal in origin and consequently could not be expected to produce carcinomas. The matter may be briefly restated:

Experiments by previous workers have shown that when vital dyes in solutions are introduced into the blood stream of animals the dyes are instantaneously picked up (phagocytosed) by one variety of cells in a specific manner, being deposited in the cellular cytoplasm as fine and coarse granules. Likewise, certain lipoids (cholesterol, olive oil) introduced per os or parenterally are attacked essentially by the same large phagocytic cells—the macrophages which dispose of this substance in a way similar to that of the dye. An interesting feature in this process is the prompt morphologic changes and also the rapid proliferation of these cells.

When I made injections of oils and dyes, respectively, into the lungs of rabbits or cats by way of the trachea, the cells found alongside the wall of the air sacs responded in exactly the way the macrophage does elsewhere in the body, that is, by instantaneous proliferation and also by phagocytosis of these substances.

Further experiments<sup>8</sup> were conducted with the anthrax bacillus, an emulsion of which in physiologic solution of sodium chloride was injected into the animal's lungs by way of the trachea. This micro-organism was chosen because of the ease with which it can be demonstrated in tissues and, what is more important, because it is infallibly pathogenic to laboratory animals. The experiments have shown that the intratracheal route of infection causes no disease, provided the skin or the subcutaneous tissues of the animal are spared from contamination. Investigation of tissues from the rabbits so infected has disclosed that the pathogenic micro-organism is retained by the pulmonary tissue where it is destroyed within a short time after the injection. As in the previous experiments with the vital dye and with the oil, the bacillus is instantaneously attacked by the local macrophages normally harboring the pulmonary septums, and also lining the wall of the air sacs which rid the tissue of the germ by way of phagocytosis.

Investigation made on human lungs likewise shows that the air sacs are in all probability lined not by epithelial cells, but by macrophages scattered in groups along the alveolar walls. In my opinion, these cells

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7. Fried, B. M.: I. The Origin of Histiocytes (Macrophages) in the Lungs, *Arch. Path.* **3**:75 (May) 1927; II. The Defensive and Metabolic Apparatus of the Lungs; The Lungs and the Macrophage System, *ibid.* **6**:1008 (Dec.) 1928.

8. Fried, B. M.: The Infection of Rabbits with the Anthrax Bacillus by Way of the Trachea, unpublished data.

are mesenchymal in origin and therefore could not give rise to an epithelial malignant disease (fig. 4).

If one therefore excludes the alveoli as a possible source of carcinoma, there remain to be considered the mucous glands and the bronchi.

#### CANCER ORIGINATING FROM THE MUCOUS GLANDS

The mucous glands are structures that lie underneath the bronchial membrana basalis; indeed, being made up of epithelial cells, they are

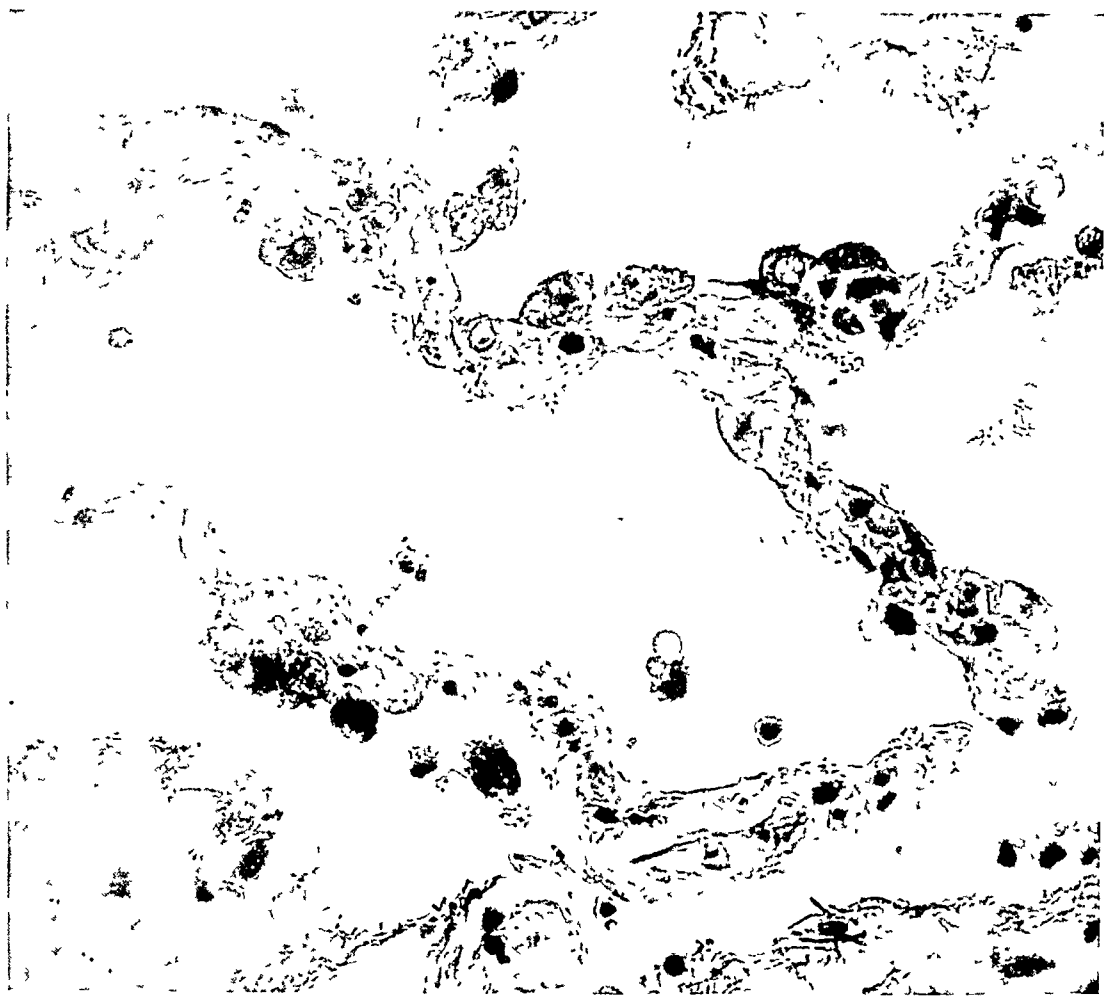


Fig. 4.—Section of human lung taken from a distended pulmonary alveolus, showing cells along the septums which to all appearances are macrophages. There is no epithelium lining the wall of the air sacs.

theoretically considered as being liable to be transformed into an epithelial malignant new growth. However, Letulle<sup>2</sup> did not include such a variety of tumors in his classification; moreover, the few cases reported in the literature in which the condition was believed to originate from these units are wholly unconvincing. No worker has ever observed

an early cancer of this kind, and the criteria, such as the glandular structure as well as the presence of mucus, which are claimed to be characteristic of these neoplasms, in reality distinguish a great many tumors originating from organs which normally form no mucous material.

The foregoing clinical, pathologic and experimental observations point toward the conception that primary carcinoma of the lungs is only bronchiogenic in origin (fig. 5).

#### REGENERATION OF BRONCHIAL EPITHELIUM AND PULMONARY CANCER

The causal and formal genesis of cancer in general and that of the lungs is a matter of dispute. Apparently a malignant disease in the



Fig. 5.—Primary bronchiogenic cancer. The cut surface of the dorsal aspect of both lungs. Tumor is seen in the first branch of the left bronchus beginning at the level of the division of the main bronchus into the two branches (indicated by arrow). The main stem of the left bronchus which enters the lower lobe, and its ventral and dorsal branches show no pathologic condition. The tumor invaded the lymph nodes. The lungs also show atelectatic areas.

lungs results from the "cancerization" of the somatic cell. This probably occurs in several ways. First, individual cells may acquire the disease, leading to their anarchic growth. Second, a local malignant condition may possibly be due to a systemic bodily imbalance of some kind. It is, moreover, probable that both conditions are required for



the development of the malady. Be that as it may, many observers are still uncertain whether a fully differentiated epithelial cell is liable to become cancerous.

It is well established that one of the factors leading to the development of a cancer is chronic inflammation, namely, irritation which causes degeneration of cells eventually followed by an excessive regeneration. However, in the lungs the columnar epithelial cells lining the bronchi have never been observed to be in a state of regeneration as evidenced by mitoses and proliferation.

Ribbert<sup>9</sup> was probably the first to emphasize the fact that neoplasms usually originate from cells which are not fully differentiated; other pathologists stated that in every organ there exist "embryonal centers" (physiologic centers of proliferation) which serve as a point of departure for tumors. The problem is complicated in that with the methods of observations at the present time the actual metamorphosis of a somatic cell into a malignant cell has never been observed. The skepticism is therefore based on the observation: (1) that a fully differentiated cell is generally "apotent," and (2) that regeneration, which is a forerunner of a malignant condition, is performed in most instances by cells other than those which appear at first glance to be affected by the noxious agent. The skin is an interesting example in this respect. In the presence of damage to this structure, regeneration of the cutaneous tissue will occur by virtue of the basal cells only, which are probably postembryonic undifferentiated cells; but when these cells, too, have been damaged, a skin graft is required for the repair of the defect.

The lining of the bronchi and their divisions is made up of three different types of cells: columnar ciliated cells, goblet cells and finally basal cells, a variety of small oval cells having a narrow cytoplasm and a nucleus rich in chromatin. The last mentioned cells lie close to the basal membrane; they do not form an uninterrupted syncytium as is observed in the skin, but are irregularly scattered here and there forming cellular agglomerations. Observation reveals that in the respiratory tract the process of regeneration takes place by virtue of the just mentioned "basal" cells, which are apparently endowed with latent developmental potentialities.

In chronic bronchopulmonary diseases accompanied by damage of the bronchial epithelium, one often notices that instead of the ciliated epithelium there appear cuboidal cells superimposed by many layers of "transitional" epithelial cells which have originated from the preexisting "basal" cells. Likewise, in chronic inflammation, these cells have

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9. Ribbert, H.: *Lehrbuch der allgemeinen Pathologie und der Pathologische Anatomie*, Leipzig, 1905.

a tendency to invade the pulmonary alveoli lining their wall, thus giving the impression that the air sacs are normally lined by cuboidal epithelial cells. They also not infrequently invade tuberculous cavities, where they ultimately become cancerous. Similarly, in cirrhotic lungs one finds wide strands of fibrous tissue containing alveolar-like structures lined by cuboidal cells. This, too, was erroneously described as pulmonary alveoli lined by alveolar wall cells which had "reclaimed" their embryonic cuboidal aspect ("regressive metaplasia"). Askanazy described an instance in which the "basal" cells proliferated to such a degree as to invade the bronchial mucous gland. I have observed

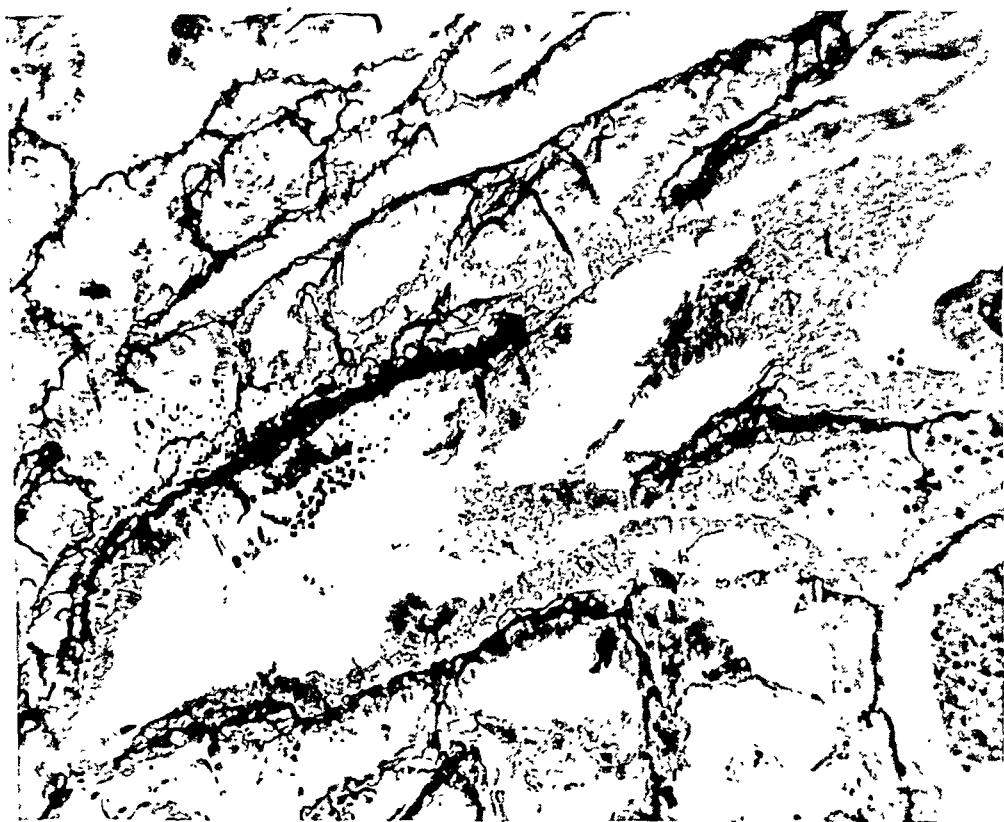


Fig. 6.—Section of cat's lung following intratracheal injection of liquid petrolatum. It was stained by Perdrau's silver nitrate method. The peribronchial alveoli are invaded by proliferated basal cells which line the alveolar septums, giving the impression that the air sacs are normally lined by cuboidal epithelium.

the same picture in experiments on cats and rabbits with the intratracheal injection of oils. In all instances, when the ciliated columnar cells were destroyed or damaged, the "basal" cells only showed active regeneration (mitoses and proliferation); they formed many layers of small cuboidal or "oat" shaped cells and also invaded the peribronchial alveoli (figs. 6 and 7).

Experimental and clinical investigation show that cancer is always preceded by a process of regeneration. The development of epithelioma

in areas subjected to roentgen rays, epithelioma of the lip of those who smoke pipes, and tar and paraffin cancers are widely known. Observation has shown that cancer of the lungs, too, usually follows a long-standing chronic inflammation. Ewing,<sup>1</sup> for instance, expressed the belief that the chief etiologic factor of carcinoma of the lungs is tuberculosis, and other observers found it in patients with bronchiectasis, and with pulmonary syphilis. Tuberculosis, syphilis and other long-standing pathogenic infections of the lungs, such as chronic inflammatory processes, cause damage of the bronchial mucosa followed by excessive (pathologic) regeneration which eventually leads to the development of an epithelial malignant disease.

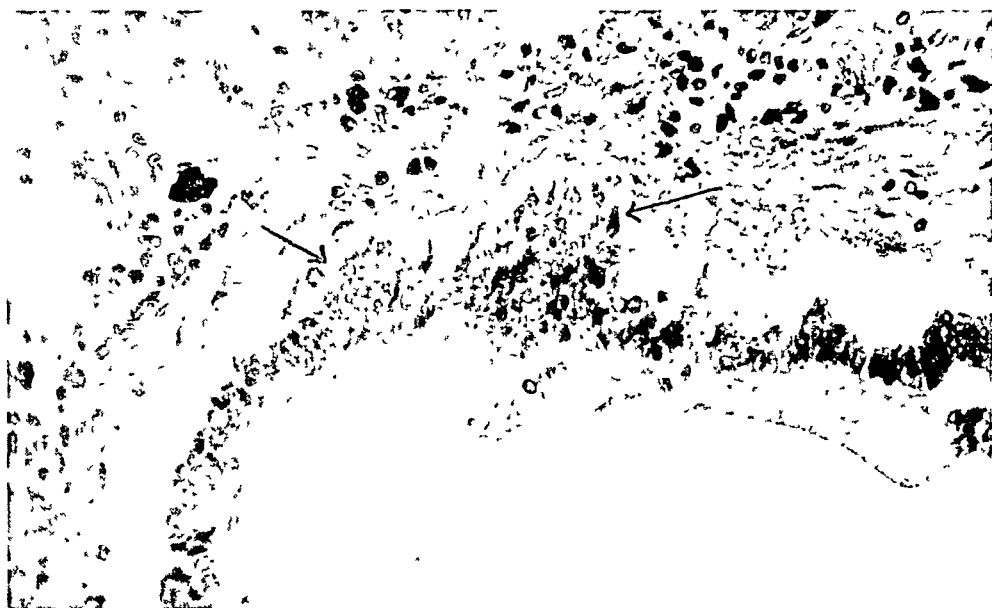


Fig. 7.—A section from a human bronchus, showing the early stage of basal cell proliferation. The peribronchial tissue shows signs of inflammation. The bronchial mucosa is detached from the basal membrane which is edematous, being invaded by small lymphocytes. The cellular agglomerations indicated by arrows are regarded as the beginning stage of protoplasia (metaplasia).

The apparent lack of any activity in the process of bronchial repair on the part of the ciliated columnar epithelium in the presence of an active "basal" cell proliferation seems to me to favor the conception that only the latter cells are concerned in the genesis of an epithelial malignant disease in the lungs.

#### METAPLASIA AND PULMONARY CANCER

Postmortem material reveals that a large percentage of all pulmonary tumors are of the basal or the squamous cell type. Since normally such cells are absent in the lungs, the origin of these tumors was said to be due to a conversion of the ciliated columnar cells into the squamous

epithelial variety. The condition was therefore designated as metaplasia (fig. 8). This conception of a direct transformation of one "well characterized tissue into another equally well characterized but morphologically and functionally different" was advanced for the first time by Virchow.<sup>10</sup> This hypothesis, however, is not borne out by close observation. In the first place, as already noted, it is improbable that the "apotent" ciliated columnar epithelium is able to transform itself into

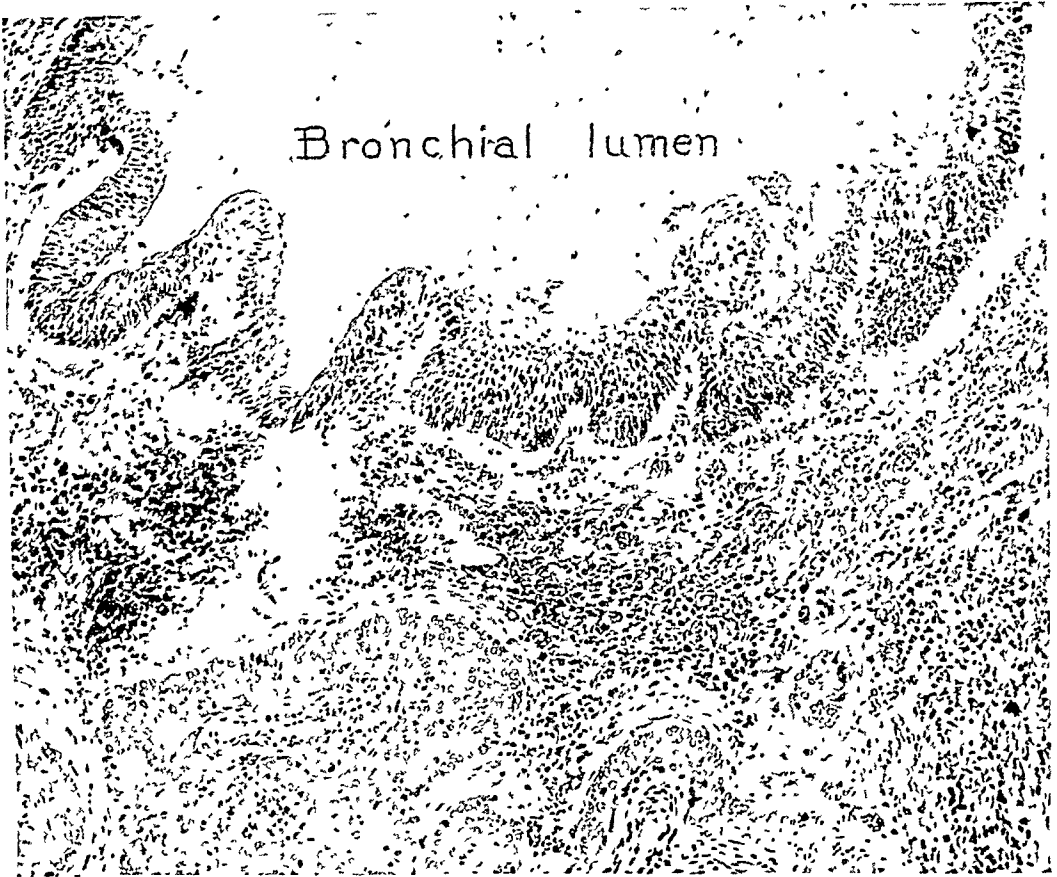


Fig. 8.—Metaplasia of bronchial epithelium in a human lung. The bronchial mucosa is made up of a layer of cells closely resembling that of the cutis. In another segment the mucosa of the same bronchus shows active proliferation of basal cells with mitoses. The membrana basalis is dissociated and largely obliterated. The tissue between the cartilaginous plates and the basal membrane is edematous, contains newly formed blood spaces, and is heavily infiltrated with lymphocytes and plasma cells. In three small bronchioles surrounded by the inflamed tissue, the lining shows a malignant condition. Hematoxylin and eosin;  $\times 110$ .

any other variety of cell. Another point was raised by Wells,<sup>11</sup> who said:

10. Virchow, R.: Ueber Metaplasie, *Virchows Arch. f. path. Anat.* **97**:410, 1884.

11. Wells, H. G.: Primary Squamous-Cell Carcinoma of the Kidney as a Sequel of Renal Calculi, *Arch. Surg.* **5**:356 (Sept.) 1922.

The formation of metaplastic squamous epithelium brings forward two puzzling topics, one chemical, the other embryologic. The chemical peculiarity is that squamous epithelium is characterized by the formation of keratin, which is a definite chemical compound, formed normally, as far as is known, by the cells of ectodermal origin, including the neurokeratin of the central nervous system. When cells of endodermal origin, such as those lining the renal pelvis or the uterus, take on the function of forming this peculiar, insoluble, sulphur-rich, indigestible, protective chemical, keratin, they have assumed a chemical function which seems to be far removed from their normal capacity. Hence we must conclude that metaplasia involves not only a morphologic but a chemical transformation of cells.

For tumor pathology, another problem arises. When cells assume the proliferative activity that is characteristic of malignant disease, they usually lose their more recently acquired functions and retake chiefly the simple vegetative function of proliferation. But when a transitional or columnar epithelial surface becomes squamous through metaplasia, and the same protracted irritation that produced the metaplasia continues until cancer results, we find that the newly acquired property of forming keratin has become fixed and the cancer is a keratinizing, squamous cell carcinoma. One would expect the epithelium to approach its original, simpler embryonal character, rather than exhibit and return so profound and recently acquired an alteration as the production of keratin.

At the present time, the original conception of Virchow<sup>10</sup> of a direct metablasia has received a new interpretation: Observers emphatically deny the authenticity of a direct transformation of the endodermal columnar cell into an ectodermal squamous epithelial cell. Borst,<sup>12</sup> for instance, stated that there is no such thing as direct metaplasia with the persistence of cells, and other workers affirmed that only those cells which are endowed with "dormant" developmental potentialities may undergo new changes. Those cells, however, which have become entirely "apotent" do not regenerate and still less become transformed into a new cellular type. Most pathologists regard the so-called metaplasia as a complicated biologic process of regeneration with new formation of cells (neoplastic phase) which is ultimately followed by a differentiation (metaplastic phase). Cells with embryonic or postembryonic potentialities are liable to such a metamorphosis, whereas the ciliated columnar epithelium lining the bronchi is a fully differentiated and therefore a "nonreversible" cell.

What then, is, the origin in the lung of the "foreign" squamous epithelial cells?

The idea of a few observers that this cell is apparently an embryonic rest could not be corroborated by most diligent investigators. Clinicopathologic and experimental studies convincingly point to another source. It would appear that the "basal" cells already referred to,

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12. Borst, M.: *Allgemeine Pathologie der malignen Geschwülste*, Leipzig, S. Hirzel, 1924: *Das pathologische Wachstum*, in Aschoff: *Pathologische Anatomie*, Jena, G. Fischer, 1923, vol. 1, p. 582.

which lie close to the membrana basalis of the bronchus, are the progenitors of the stratified squamous epithelium.

Teutschländer<sup>13</sup> observed the process of "transformation" of this cell in the bronchi of rats that died of bronchopneumonia; Goldzieher<sup>14</sup> found it in the lungs of children who died of diphtheria and measles,

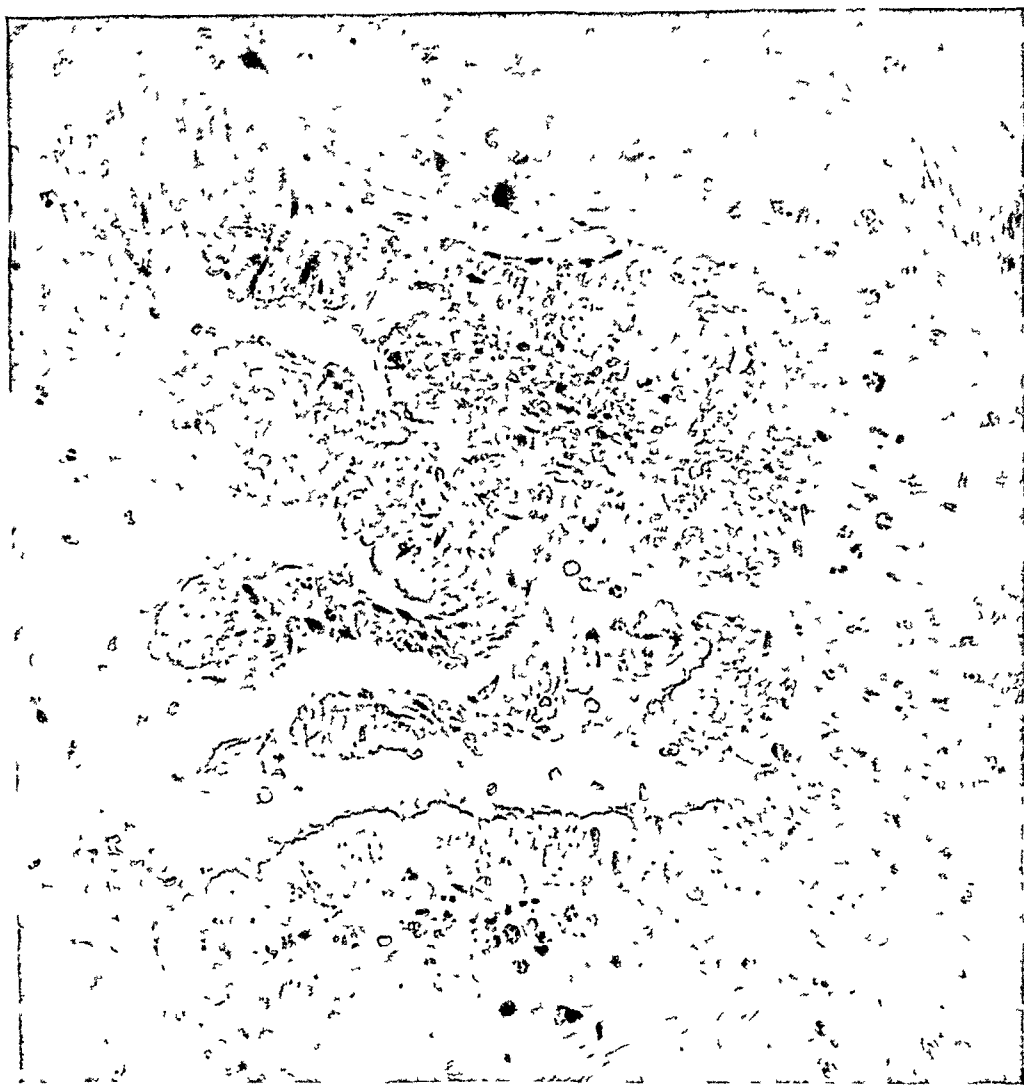


Fig. 9.—Protoplasia of bronchial epithelium of human lung. The ciliated columnal epithelium is pushed away by the protoplasmic basal cells which are agglomerated in masses. The columnar epithelium shows no signs of regeneration, as evidenced by mitoses and proliferation.

13 Teutschlander: Ueber Epithelmetaplasie mit besondere Berücksichtigung der Epidermisierung der Lungen, *Centralbl. f. allg. Path. u. path. Anat.* **30**:433, 1919

14. Goldzieher, M.: Ueber Bazalzellwucherungen der Bronchialschleimhaut, *Centralbl. f. allg. Path. u. path. Anat.* **29**:506, 1918.

and Askanazy<sup>15</sup> outlined this pathologic phenomenon in the lungs of persons who died of pneumonia following influenza.

Of particular interest are the experimental studies by Wolbach<sup>16</sup> on changes in the tissues following deprivation of fat-soluble vitamin A. By feeding rats a deficient diet, he noticed that the "missing factor" caused a widespread keratinization of epithelium. In the respiratory tract the process began in numerous foci, and the rate of the cellular growth was rapid as attested by numerous mitoses of the basal cells. What is more, these experiments have shown that the basal cells begin to proliferate even before any changes are detectable in the columnar epithelium which only subsequently degenerates and separates from the basal membrane. It is also interesting that this process is not necessarily brought forward by a previous inflammation; a mere stimulus generated by a "missing factor" from the food caused an "alarm" among the cells, followed by their multiplication and differentiation.

Apparently this pathologic phenomenon occurs in numerous bronchopulmonary diseases. Askanazy<sup>15</sup> found metaplasia in a high percentage of patients who died of pneumonia following influenza, and Goldzieher<sup>14</sup> noticed the same thing in patients with measles and diphtheria. In a recent study, Smith<sup>17</sup> also observed metaplasia in children with whooping cough. Two examples of this condition, one an early stage of the condition and the other a fully developed metaplasia, have recently been observed. The first was in a girl, aged 17 years, who died of aleukemic lymphadenosis. The lungs contained numerous bacteria, and the alveoli were in areas filled with fibrin. The bronchi showed numerous polymorphonuclear leukocytes, desquamation of the columnar ciliated epithelium and a proliferation with transformation of the basal cells into transitional cells (figs. 7, 9 and 10).

In the second example of a thymoma with pulmonary metastases, the lungs showed a great deal of fibrosis and round cell infiltration. The condition found in many bronchi is demonstrated in figure 9. From this picture it will be seen that the "basal" cells only have proliferated, while the columnar cells are merely pushed away.

The peculiar character of the differentiation of these cells into squamous epithelium is interpreted in the light of the ontogenesis of the tissue in question. From an embryologic standpoint the tracheo-bronchial tree and the esophagus represent two sister organs, and their

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15. Askanazy, J.: Ueber die Veränderungen der grossen Luftwege besonders ihre Epithelmetaplasie bei der Influenza, *Cor.-Bl. f. schweiz. Aerzte* **49**:465 (Jan. 18) 1919.

16. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamin, *J. Exper. Med.* **42**:753, 1925; Vitamin A Deficiency in the Guinea-Pig, *Arch. Path.* **5**:239 (Feb.) 1928.

17. Smith, Lawrence W.: The Pathologic Anatomy of Pertussis, *Arch. Path.* **4**:732 (Nov.) 1927.

development goes parallel. Schridde<sup>18</sup> has produced evidence to show that in the earliest stages of development the esophagus is lined with one layer of cuboidal cells, which at the fifth week becomes doubled and at the tenth acquires goblet cells and ciliated columnar epithelial cells. Whereas in the bronchi the development ends at this phase, in the esophagus these cells degenerate and desquamate, being subsequently replaced by a transitional epithelium and finally by a stratified squamous epithelium. It is assumed, then, that in pathologic processes the

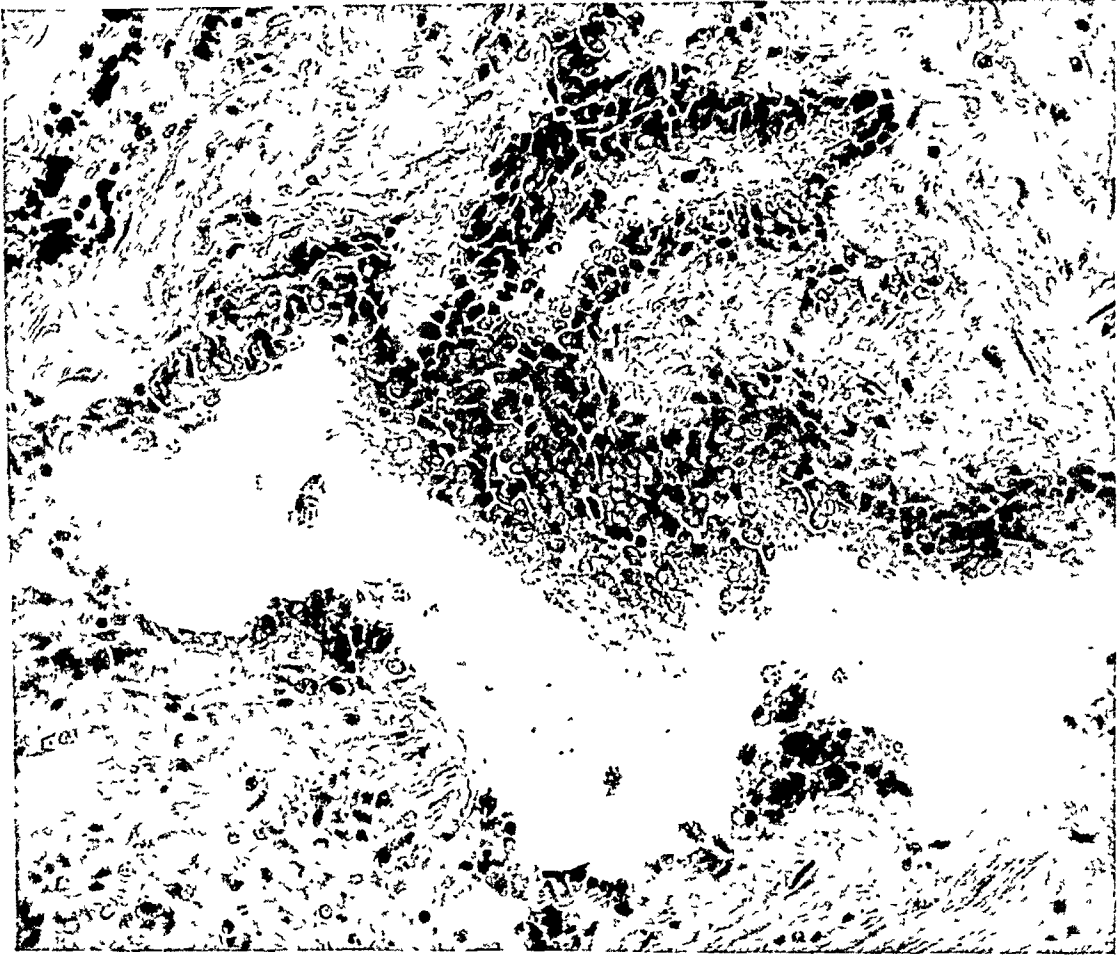


Fig. 10.—Protoplasia of bronchial epithelium. Section from a human bronchulus respiratorius, first order, showing proliferation of the basal cells forming many layers of stratified squamous epithelium. The bronchiolar basal membrane being destroyed, these cells invade the surrounding granulation tissue where they are arranged in a tubular manner. Methylene blue and eosin;  $\times 300$ .

bronchus, in its regenerative attempt, merely reaches in adult age the stage which the esophagus has attained as an embryo.

It will be seen, therefore, that the process is not a transformation of the adult columnar epithelium into a squamous type, but that a

18. Schridde, II.: Die Entwicklungsgeschichte des menschlichen Speiseröhren Epithels, Wiesbaden, 1907.



development of undifferentiated cells followed by proliferation and differentiation occurs. The phenomenon is consequently not that of metaplasia, but is one of protoplasia (indirect metaplasia).

Briefly, then, the process of repair or regeneration in the bronchi is performed by the bronchial "basal" cell only. In physiologic repair, these cells differentiate merely into the normal lining of the bronchus. But when the process is pathologic, their fate depends in all probability on the nature of the stimulus. Thus, they may differentiate into metaplastic islands and so remain indefinitely, or they may develop into a malignant condition. In fact, most pathologists regard the phenomenon of metaplasia as being a precancerous stage.

#### REPORT OF CASES

Two patients with primary carcinoma of the lungs came to my attention: In one the histology of the tumor was that of a basal cell cancer; in the other, it was a typical keratinizing epidermoid carcinoma.

*CASE 1.—History.*—A man, aged 38, a gardener, entered the hospital with the complaint of progressive weakness and loss of weight of eight months' duration. The past and family histories were unimportant.

One week before admission, swelling was noticed in front of the left shoulder. For three or four weeks, he had a cough coincident with a cold, and raised slight quantities of normal-looking sputum. He became so weak that he could hardly sit up in bed. He had been hoarse for a month. He had noticed clubbing of the fingers, of the left hand particularly, during the last two weeks.

*Examination.*—Evidences of loss of weight and cachexia were found. Edema involved the left shoulder and the apical regions. The expansion of the chest was less marked on the left. Respirations were 26, and of shallow depth. The thorax was narrow and ptotic; the heart and aorta showed no pathologic condition. The veins in the left arm and neck were dilated, and slight dilatation was present in the right arm.

In the lungs, the expansion was diminished on the left side. Vocal fremitus was diminished on the left side and was practically absent posteriorly. On percussion of the left side, the note was flat from the apex to the angle of the scapula, and dull down to the lower border and to the posterior axillary line. Anteriorly, it was dull at the apex, up to the second interspace; below that, it was normal for an interspace and then markedly tympanitic up to the base and along the axillae, as if there were air beneath the pleural cavity. On auscultation, the left side showed diminished bronchial breathing posteriorly at the apex down to the scapula. Below that, for a distance of two or three interspaces, the breath sounds were purely bronchial and close to the ear; at the base, there was distant bronchial breathing. The whispered voice corresponded to the breath sounds. Anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base there was distant bronchial breathing. The right side did not show any pathologic condition. The voice did not sound abnormal. Except for the clubbed fingers, which were more marked on the left, the physical examination revealed nothing remarkable.

During thoracentesis, a few small pieces of necrotic material were obtained which on examination showed the presence of carcinoma.

The patient died after a stay of twenty-two days in the hospital.

*Necropsy.*—The body was poorly nourished and cachectic, measuring 170 cm. in length. The external examination revealed clubbed fingers, more pronounced on the left hand; a large decubitus over the sacrum; a slightly prominent abdomen, and a hard, palpable lymph node in the right axilla. The peritoneal cavity contained 150 cc. of clear, straw-colored fluid. A membranous exudate about 2 mm. thick was found overlying the lower portion of the sigmoid colon.

*Pleural Cavities:* The right cavity was free and contained about 100 cc. of a clear yellowish fluid. Both the parietal and the visceral pleurae showed no



Fig. 11 (case 1).—Primary basal cell (nonkeratinizing) epithelioma of the left bronchus. The main stem of the left bronchus which enters the lower lobe and its ventral and dorsal branches show no disease. The first branch of the left bronchus is also normal, but its lower and middle intrapulmonary branches are patent only for about 3 cm. and are occluded at the end by tumor.

inflammatory changes or invasion by tumor. The left cavity contained about 300 cc. of fluid similar to that found on the right side. The cavity was free, except at the apex and posteriorly, particularly along the spine and posterior wall of the chest where it was obliterated by extremely strong adhesions. The left lung appeared normal in front and in the axillary region from the beginning of the third rib downward; posteriorly, only the lower lobe was free from tumor. The visceral pleura in the areas untouched by the new growth was normally thin and

translucent, and the lung was pale and slightly emphysematous. The lungs and heart were separated from the pleural cavity *en masse*.

Owing to strong adhesions, the apical part of the tumor and that part along the spine were torn on removal, a portion being left in the chest. When the visceral pleura was thus torn, it seemed that the tumor walled off by the pleura shelled out from the latter and appeared twice as large as when seen in situ. The tumor was grayish white, moderately firm and somewhat friable. It was composed of one large mass, and on the surface in front, two nodules, from 3 to 5 cm. in diameter, were seen. The tumor was sharply demarcated from the pulmonary parenchyma.

Trachea and Bronchi: The trachea appeared normal. Its mucosa was pale and covered with a colorless, frothy fluid. The right bronchus and its divisions showed no changes. The main stem of the left bronchus entered the lower lobe of the lung as usual, and its dissected ventral and dorsal branches were patent and showed no pathologic condition. The first branch of the left bronchus (normally distributed to the superior lobe) was normal throughout. Two of its larger intrapulmonary branches, the lower and middle, were patent and appeared normal only for about 3 cm. and were occluded at the end by tumor. The other intrapulmonary branches distributed in the superior part of the upper lobe could not be traced at all, being entirely surrounded by tumor and destroyed.

Lymph Nodes: The tracheal, tracheobronchial and mediastinal lymph nodes did not show any invasion by tumor. The nodes below the bifurcation seemed to be enlarged, without, however, any invasion by the tumor. The third and fourth ribs at the junction of the vertebrae and two thoracic vertebrae were eroded in the areas of the tumor attachment, but no invasion of the bone could be demonstrated. The other organs did not reveal the presence of any new growth or other noteworthy changes.

*Microscopic Examination.*—Lungs: Sections taken from different parts showed the tumor to be composed of polyhedral cells having a large cytoplasm and a voluminous vesicular nucleus. These were arranged in columns and strands from 2 to 3 cells broad, which showed anastomosis and branching. In one section, the cells had a somewhat tubular arrangement; their nuclei were compressed, pushed toward the periphery and had a rosetlike appearance. In another section, the tumor was rather solid, being arranged in small clumps of cells or short rows of single cells. The cells contained a great variety of inclusions, resembling in areas the "parasites" described by some writers and, occasionally, the so-called "bird's eye" inclusions. Round globules of a different size, stained black with methylene blue eosin, were conspicuous all over the sections. There was no keratinization or pearl formation. A great deal of fat was seen in the cells, as well as between the cells.

The stroma of the tumor consisted of a loose, edematous connective tissue infiltrated with small round cells, and here and there with single tumor cells. The tumor was sharply demarcated from the pulmonary parenchyma, which showed compression of the alveoli and thickening of the alveolar wall. Mitotic figures were rarely seen. The lymph nodes showed no signs of tumor. The other organs, except for the kidneys, which showed an early parenchymatous nephritis, were not remarkable (figs. 12 and 13).

The pathologic diagnosis was basal cell carcinoma of the left lung originating in a small division of the left bronchus; chronic, adhesive, fibrous pleuritis; hydrothorax (bilateral); peritonitis; decubitus, clubbed finger and cachexia.

*Comment.*—The histologic and clinical features of the tumor in this case were that of a typical (nonkeratinizing) basal cell cancer. Like most basal cell cancers of the skin, the present tumor did not metastasize,

being, therefore, relatively benign. It is interesting whether a pulmonary cancer of this variety would be as sensitive to radium or to roentgen rays as is the cutaneous new growth with a similar structure. The bronchiogenic origin of these tumors is at present accepted by most pathologists. Its peculiar microscopic appearance, however, as referred to, is attributed to a transformation of the columnar ciliated epithelium, which is apparently an error. Indeed, the lungs in this case were examined at a period when the tumor was in an advanced stage, which made histogenic studies futile. Nevertheless, the microscopic architecture and

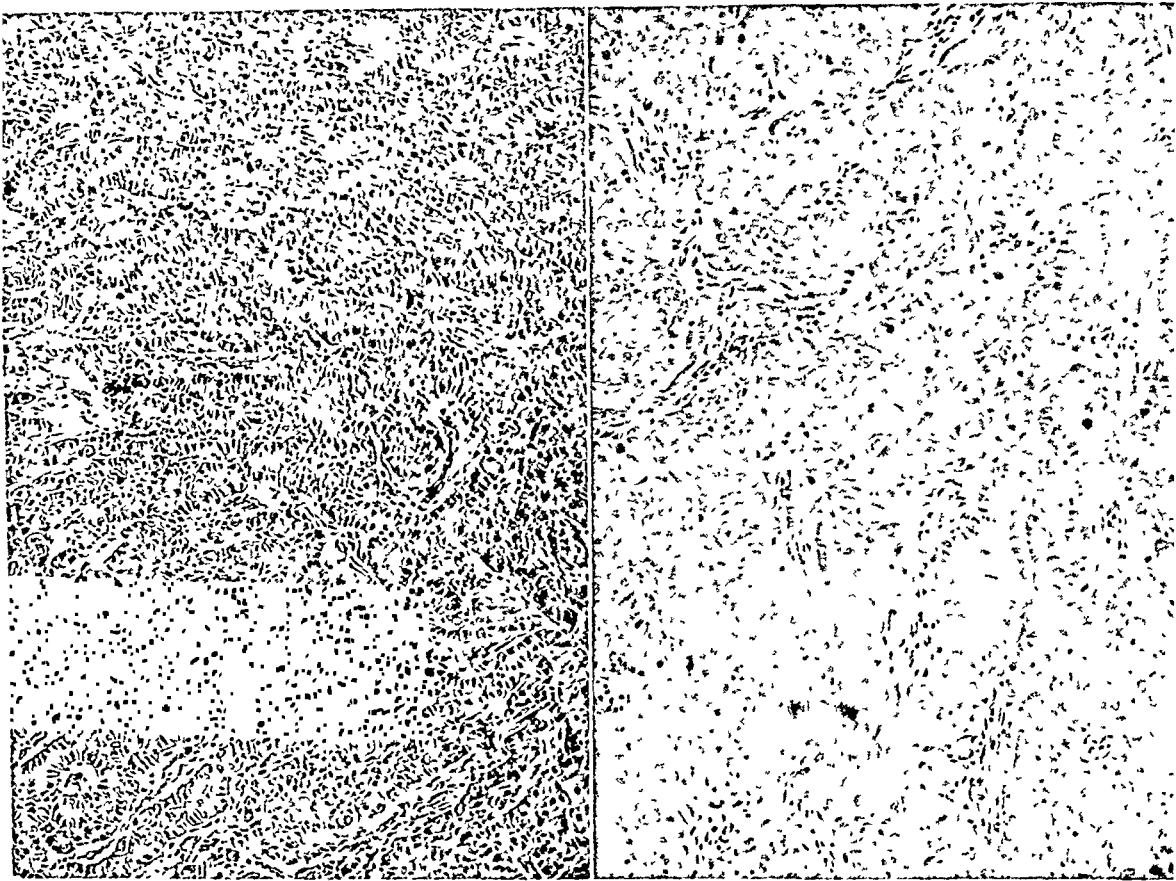


Figure 12

Figure 13

Figs. 12 and 13 (case 1).—Primary basal cell (nonkeratinizing) epithelioma of the left bronchus. The tumor is composed of polyhedral cells arranged in columns and strands which anastomose and branch. They also form "tubules." The gross appearance of the tumor is given in figure 12.

the clinical characteristics of the growth, when added to the biologic potentialities of the bronchial basal cell, seem to favor the opinion that the cancer did not originate through metaplasia from the ciliated columnar epithelium, but developed as a result of protoplasia of the undifferentiated basal cells of the bronchial mucosa.

In the following case the differentiation of these cells went one step further, leading to a typical keratinizing squamous cell carcinoma.

CASE 2.—*History*.—A man, aged 64, entered the medical service of the hospital, complaining of cough and fever. Fourteen months before, he had some wheezing and shortness of breath, which lasted for about six months. He entirely recovered from this and was well until six months before admission, when he began to have an unproductive but distressing cough which varied with the weather; the cough grew worse during a cool spell and was increased by exertion. This condition had continued; there was little sputum, but on one occasion the patient had hemoptysis. The only pain he had had was substernal and in the epigastrium after paroxysmal coughing. He had lost 10 pounds (4.5 Kg.) in the last year. The roentgen examination two months previous to admission to the hospital showed a rounded shadow just to the right of the heart shadow, suggestive of a mediastinal tumor.

*Examination*.—Dulness was present over the right lower lobe with increased breath sounds, normal whispered voice and decreased tactile fremitus in this area. The heart was apparently displaced to the right. The temperature ranged between 99.8 and 103.8 F.

The roentgen examination on entrance showed marked clouding of the right base. The heart, trachea and mediastinum were displaced to this side. The "rounded shadow" originally noted was not evident, apparently being obscured by the heart shadow.

The patient remained in the hospital twenty-two days during which time he lost about 10 pounds (4.5 Kg.). Except for signs of a slight amount of fluid in the right side of the chest, the clinical picture did not change. He was discharged, three weeks after admission, unimproved.

Two weeks later, he was readmitted to the hospital. On physical examination, no marked changes were noted. The patient remained in the hospital three days, and was discharged with the diagnosis of carcinoma of the lungs. At home, he developed occasional hemoptysis. The cough and fever continued. He died about two years after the onset of the first symptoms.

*Necropsy*.—The necropsy was performed by Dr. S. B. Wolbach, fifteen hours post mortem. The body was poorly nourished and did not show any marks worthy of note. The peritoneal cavity, except for the presence of about 750 cc. of clear yellow fluid, was not remarkable. The pericardial cavity was distended with about 150 cc. of a dark red fluid, containing flecks of fibrin. The pericardial surfaces were covered with a red, shaggy, adherent, fibrinous material. The heart was normal in size. The striking feature of the organ, in addition to the fibrinous exudate, was the presence of about fifteen elevated nodules from 4 to 12 mm. in diameter, which were distributed fairly uniformly over the right and left ventricles. On incision they were white, fairly firm and regular, and pressure caused droplets of white material to exude, which subsequent microscopic examination showed to be keratinized and necrotic epithelial cells.

*Chest*: The ribs and sternum were adherent on the right side to a thickened pleura along the anterior border of the right lung, and to a hard, firm mass overlying the ascending aorta. The tissues at the anterior mediastinum were edematous. The right pleural cavity was entirely obliterated by dense tissue. The left cavity was free and contained about 1 liter of clear, deep yellow liquid.

*Lungs*: The right lung was freed by stripping the parietal pleura, and the lungs and heart were removed *en masse* with the right side of the diaphragm. The pleura over the posterior border of the right lung ranged from 3 to 6 mm. in thickness, and consisted of dense, white, fibrous tissue with firmer white plaques, from 2 to 4 mm. thick, composed of friable tumor material. There were a few pigmented lymph nodes at the anterior border of the diaphragm which contained numerous white nodules.

When the trachea and bronchi were opened, the trachea, except for deep injection, was normal. The left primary bronchus also was normal. The right was practically occluded 2 cm. below the bifurcation (fig. 14). Anteriorly, the wall of the right primary bronchus was replaced by a friable, white tumor tissue which on pressure exuded soft, white material; on subsequent examination this proved to contain desquamated epithelial cells, the largest part of which were keratinized. The only branch of the right primary bronchus that could be found was one leading to the upper part of the right lobe, and the orifice of this bronchus



Fig. 14 (case 2).—Primary squamous cell epithelioma (keratinizing) of the right bronchus, showing the dorsal aspect of both lungs, trachea and main bronchi. The tumor is present in the right bronchus and the right lung. The left bronchus is indicated by the arrow.

was nearly completely occluded by tumor tissue. Below, the bronchus ended abruptly in a mass of friable tumor, from 1 to 3 cm. thick, which extended downward along the inner posterior margin of the lung for a distance of 8 cm. Anteriorly, the tumor, which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta, forming a layer 1 cm. thick, which extended upward over the ascending portion of the arch. Two parallel incisions were made through the posterior borders of the lungs and showed that the whole lung was atelectatic, with here and there small bronchiectatic cavities. The whole of the upper lobe was tough and fibrous, and in the

peripheral portion of the lung were a few nodules, a few abundant in the lower lobe. The left lung was not incised but seemed to be normal. On the inner surface of the lower lobe, that is, in contact with the pericardium, there were two plaques of tumor, each a few millimeters thick and 1 cm. wide. The head was not opened. The other organs were normal.

*Microscopic Examination.*—Lungs: The tumor grew without any definite arrangement. Nests or masses of cells were scattered over the sections surrounded

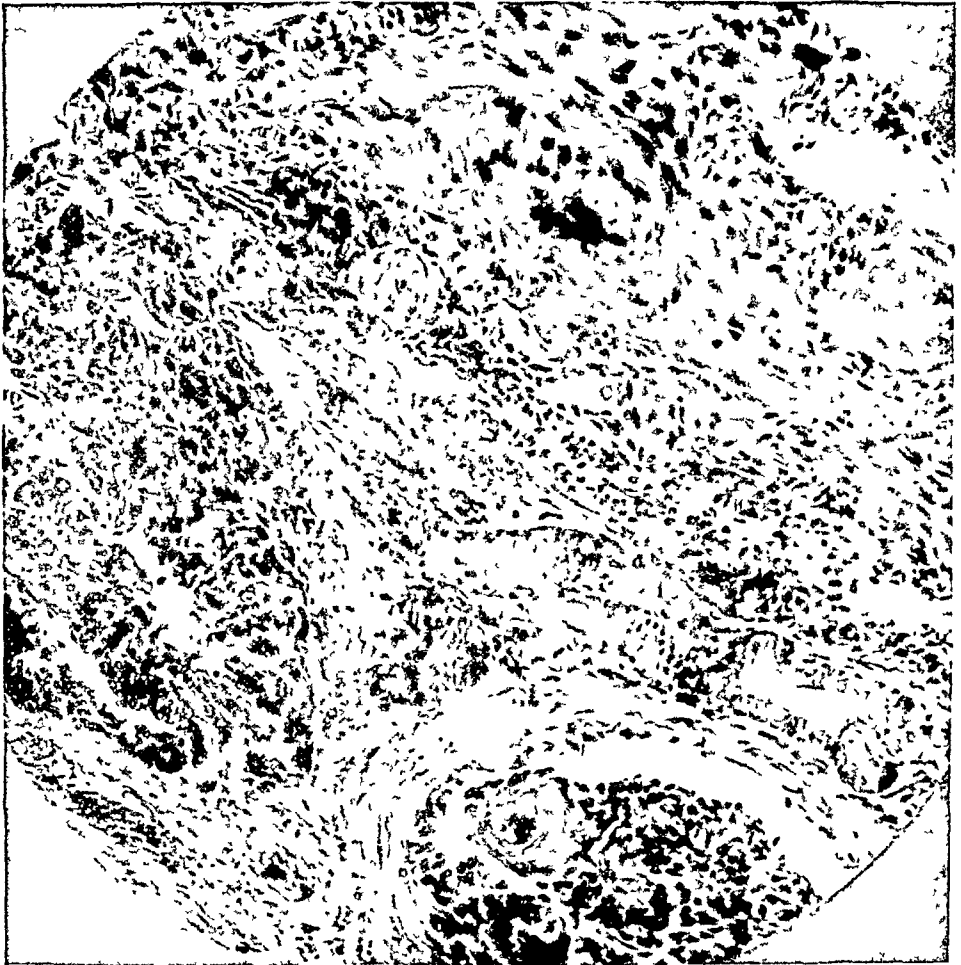


Fig. 15 (case 2).—Primary squamous cell (keratinizing) epithelioma of the right bronchus. The tumor cells are arranged in nests without any definite architecture. They show areas of keratinization and "pearl" formation. The gross appearance of the tumor is shown in figure 14.

by thick bands of dense fibrous tissue. The tumor cells individually were large, polygonal or elongated and irregular in outline. The cytoplasm was finely granular and stained blue. The vesicular nucleus occupied the greater part of the cell; it was large, rich in chromatin and contained a centrally located, deep stained nucleolus. The cells varied slightly in size. Large cells with many nuclei, resembling giant cells, were encountered here and there. In many areas, mostly in the center of the tumor mass, the cells had a tendency to arrange themselves in concentric layers. Here, the cells were usually larger than the tumor cells; their cytoplasm was stained deep red with eosin, and the nucleus seemed generally to

be smaller. These masses of cells had the typical appearance of the cornified epithelium encountered in the so-called "pearls" of the epidermoid carcinoma. Here, also, there was a definite tendency to "pearl" formation (fig. 15). These keratinized masses were seen in practically all sections. The pulmonary tissue adjacent to the tumor, but free from the new growth, showed extensive fibrosis in dense and avascular areas and in areas rather loose and richly supplied with blood. Macrophages loaded with a brown pigment were disseminated occasionally among the tumor cells and, more conspicuously, in the preserved and compressed or distorted alveoli. Anthracosis and round cell infiltration were seen here and there. The pleura showed invasion by a tumor which displayed the characteristics of the main tumor. The lymphatics were greatly distended by tumor nodules, which occupied the greater part of their lumen.

**Esophagus:** The tumor here was confined to the muscularis mucosa and submucosa and was identical with the pulmonary tumor. It was sharply demarcated from the normal tissue. The esophageal mucosa was intact. Mitotic figures in the main tumor, as well as in the metastases, were rarely found.

The pathologic diagnosis was epidermoid carcinoma originating in the right primary bronchus with metastases to the pleura, left lung, heart, regional lymph nodes and esophagus; hydrothorax (left); hemopericardium; ascites; amyloid degeneration of the spleen, and passive congestion of the liver.

*Comment.*—Here, then, is a cancer with histologic traits of a keratinizing epidermoid type which has led to widespread metastases. The problem of basal cell epithelioma and squamous cell epithelioma of the skin has been the source of numerous investigations. For particulars on the subject, a recent study by Montgomery<sup>19</sup> may be consulted.

Apparently in the lungs, too, this variety of cancer has its origin in the "basal" cell of the bronchial mucosa.

#### CONCLUSIONS

1. Carcinoma originating primarily in the lungs is bronchiogenic.
2. There is evidence that when the disease is found in the lungs it results from a pathologic (excessive) regeneration following chronic inflammation of the bronchial tree.
3. Of the three varieties of cells lining the bronchial mucosa, i.e., the ciliated columnar epithelium, the goblet cells and the "basal" cells, only the last are concerned in the process of regeneration of the bronchial mucous membrane. It is assumed, therefore, that these cells likewise serve as a sole matrix for primary bronchiogenic tumors.
4. Similarly, primary squamous cell epitheliomas and basal cell epitheliomas of the lungs do not result from metaplasia of the pre-existing ciliated columnar epithelium, but originate through protoplasia (indirect metaplasia) of the undifferentiated basal cell of the bronchial mucous membrane.

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19. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. 18:50 (July) 1928.



# MULTIPLE HEMANGIOFIBROMA OF THE PULMONARY VALVE \*

MILTON G. BOHROD, M.D.

CHICAGO

In 1898, when Guth<sup>1</sup> reported the third case of a tumor on a cardiac valve, he wrote: "In spite of their relative rarity there is a copious literature concerning primary tumors of the heart." From that time until this report of the twenty-fourth case the literature has grown immensely. About these small, harmless bodies and the related mural endocardial tumors much controversy has arisen, which has not yet subsided, for in Henke and Lubarsch's new "Handbuch der spezielle pathologische Anatomie," Ribbert devoted several pages to the discussion as to whether they are tumors. The discussion is all in the German literature, for, with the exception of the first few cases which were reported from France, the single report of Dean and Falconer<sup>2</sup> in England and the short report of Blumgart<sup>3</sup> in the United States, all the cases seem to have been found in Germany, Austria and Switzerland.

It is peculiar that however much these tumors may differ among themselves, they are sufficiently alike to be grouped by every one who writes about them into a single group, and that between them and the various conditions which they are supposed to resemble, there are no intermediate stages. Various referred to as myxomas, pseudo-myxomas or different kinds of fibromas, they may be divided into two groups according to location: those on the mural endocardium and those on the valves. Here the differences end, for histologically the two types resemble each other closely. The mural tumors, of which about seventy-five cases have been reported, may reach such large size as to fill an entire cardiac chamber, usually the auricle. In most cases they take their origin from the margin of the fossa ovalis. They are papillomatous, completely covered by endothelium, and are composed of loose tissue resembling myxomatous tissue. They may or may not contain many blood vessels or elastic fibers. They have been described

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\* Submitted for publication, March 8, 1929.

\* From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Guth, H.: Ueber einem Fall von papillärem Myxom auf der Valvula tricuspidalis cordis, *Pragr. med. Wchnschr.* **23**:85, 1898.

2. Dean, G., and Falconer, A. W.: Primary Tumors of Cardiac Valves, *J. Path. & Bact.* **18**:64, 1913-1914.

3. Blumgart, L.: A Tumor of the Mitral Valve, *Am. J. M. Sc.* **134**:576, 1907.

as myxomas (Ribbert<sup>4</sup>), fibromas (Jaffé<sup>5</sup>), fibro-angiomyxomas (Fabris,<sup>6</sup> Csemez<sup>7</sup>) and hemangio-elastomyxomas (Brenner<sup>8</sup>) by authors who think of them as neoplasms, and as organized thrombi by those who do not believe in their neoplastic origin (Stahr,<sup>9</sup> Gödel,<sup>10</sup> Thorel,<sup>11</sup> Schwartz<sup>12</sup>). Similar structures have been reported in animals (Stahr,<sup>9</sup> Ackerknecht<sup>13</sup>).

In twenty-three cases of valvular tumor nodules reported, five were tumors of the mitral, six of the aortic, eight of the tricuspid and four of the pulmonary valve. All of them were observed accidentally at necropsy on patients who died from other causes. The ages varied from 19 to 86 years; the cases were about evenly distributed between the two sexes. Fourteen showed no signs of cardiac disease other than the tumors, three showed slight atheromatous thickenings of the valves, one an aneurysm of a mitral cusp, and only four showed evidences of chronic endocarditis. In view of the frequency of chronic endocarditis in any large necropsy material, the last mentioned observation is not significant. In only one case was there clinical evidence of endocarditis (Leonhardt<sup>14</sup>). Most of the tumors were pedunculated, but some were adherent to the valve by a broad base. A great many of them were papillary. All of them were single growths except those in the case of Boye (quoted by Husten<sup>15</sup>) who, in an inaugural dissertation which I have been unable to obtain, reported a case of two tumors of the tricuspid valve.

Twelve of the seventeen authors who reported cases of valvular tumors considered them as true tumors. Ribbert,<sup>4</sup> especially, empha-

4. Ribbert, H.: *Geschwülstlehre*, ed. 2; Bonn, Cohen, 1914, p. 314.

5. Jaffé, R. H.: *Das Myxom des Herzens*, Beitr. z. path. Anat. u. z. allg. Path. **64**:533, 1918.

6. Fabris, A.: *Fibro-angio-myxomatöse Neubildung des menschlichen Herzens*, Virchows Arch. f. path. Anat. **241**:59, 1923.

7. Csemez, H.: *Zentralbl. f. Herz. u. Gefasskr.* **17**:304, 1925.

8. Brenner, F.: *Das Haemangioelastomyxoma cordis und seine Stellung unter den Myxomen des Herzens*, Frankfurt. Ztschr. f. Path. **1**:492, 1907.

9. Stahr, H.: *Ueber die sogenannte Endokardtumoren und ihre Entstehung*, Virchows Arch. f. path. Anat. **199**:162, 1910.

10. Gödel, A.: *Zur Kenntnis der primären Herzgeschwulste*, Zentralbl. f. Herz. u. Gefasskr. **14**:99, 1922.

11. Thorel: *Pathologie des Herzens-Lubarusch und Ostertag*, Ergebn. d. Allg. Path. u. path. Anat. **14**:11, 1910; *Pathologie des Herzens*, ibid. **17**:11, 1915.

12. Schwartz, D.: *Ueber die sogenannten Myxome des Herzens*, Virchows Arch. f. path. Anat. **264**:747, 1927.

13. Ackerknecht, in Joest: *Spezielle pathologische Anatomie der Haustiere*, Berlin, Richard Schoetz, 1919, vol. 4, pp. 317 and 466.

14. Leonhardt, A.: *Ueber Myxome des Herzens insbesondere der Herzklappen*, Virchows Arch. f. path. Anat. **181**:347, 1905.

15. Husten, K.: *Ueber Tumoren und Pseudotumoren des Endokards*, Beitr. z. path. Anat. u. z. allg. Path. **71**:132, 1923.

sized the true neoplastic nature of these bodies and thought most of them to be myxomas or angiomyxomas. He traced their origin to rests of myxomatous tissue which are sometimes found in otherwise normal valves. Authors, however, who have written about these reports have not been so unanimous. Those who consider the mural endocardial tumors as organized thrombi offer the same explanation for the valvular bodies. Thorel,<sup>11</sup> in two reviews on cardiac disease, insisted that all the cardiac masses, mural and valvular, are organized thrombi. Kirch,<sup>16</sup> who wrote the latest review on cardiac disease, steered between these two views and said that some of them may be neoplasms and others organized thrombi. Other authors (Leonhardt,<sup>14</sup> Curtis<sup>17</sup>) consider the tumors as the remains of old endocarditic lesions. The occasional discovery of concomitant chronic valvular endocarditis and the presence of lymphocytes and plasma cells within the tumors have been offered in support of their view. Zurhelle<sup>18</sup> reported a tumor-like body on the tricuspid valve the center of which was a large endothelial-lined blood space communicating with the right ventricle, the outside of which was connective tissue. He considered this growth as a persistent valvular blood cyst, such as is often found on the pulmonary valves of the new-born infant, which had become partly organized. He suggested that the organization of such persistent cysts might account for the polypoid valvular tumors. Koechlin,<sup>19</sup> who reported three cases of polypoid tumor, described in the same article thirty-five cases of Lambl's excrescences, fine, threadlike filaments projecting from the noduli arantii of the aortic valve. He expressed the belief that the valvular tumors in his case, and possibly in all other cases, were modified excrescences of this type. Leonhardt<sup>14</sup> had mentioned the same possibility several years before.

In the following case multiple tumor nodules were found on the pulmonary valve of a young man dying from abscesses of the brain. A primary focus for the latter was not discovered, so that in this instance the determination of the neoplastic or infectious nature of these tumors is perhaps of more than academic interest.

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16. Kirch, E.: *Pathologie des Herzens*, Lubarsch-Ostertag, *Ergebn. d. allg. Path. u. path. Anat.* **22**:1, 1927.

17. Curtis: *Note sur un tumeur de la valvule mitrale*, *Arch. de physiol. norm. et path.*, 1871-1872, vol. 4.

18. Zurhelle, E.: *Ueber ein aussergewöhnlich grosses persistierendes Blutknötchen an der Tricuspidalklappe eines Erwachsenen mit Bemerkungen über die Genese der sogenannten polypösen Herzklappenmyxome*, *Frankfurt. Ztschr. f. Path.* **20**:319, 1917.

19. Koechlin, E.: *Ueber primäre Tumoren und papillomatöse Exkreszenzen der Herzklappen*, *Frankfurt. Ztschr. f. Path.* **2**:295, 1908.

## REPORT OF CASE

C. A., a white man, aged 20, entered the Research and Educational Hospital in coma. The history was obtained from his parents who were unusually cooperative but who knew little about his illness, which was recent, except that he had been complaining of severe headache and dizziness. So far as they knew, he had never had complaints referable to the heart. Signs of increased intracranial pressure and persistent high temperature and leukocytosis led to the diagnosis of probable

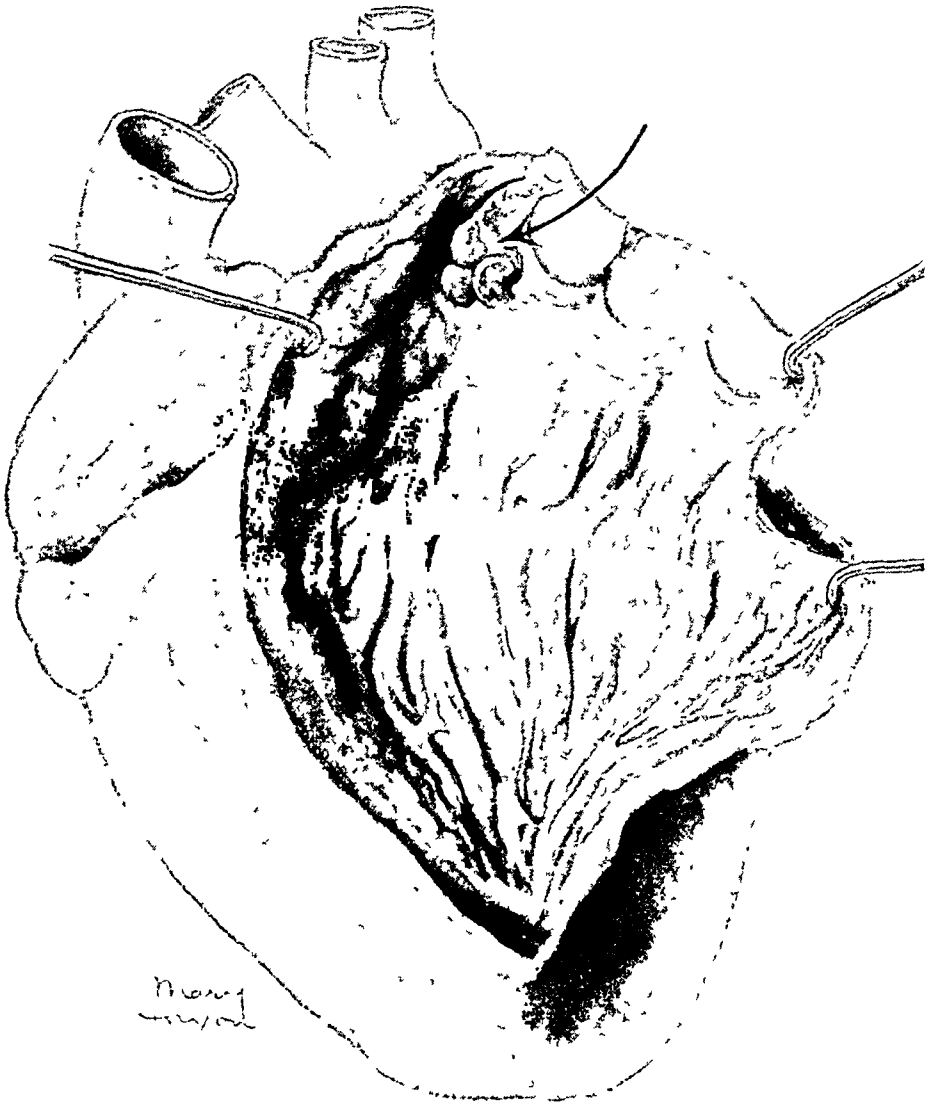


Fig. 1.—Hemangiofibroma of the pulmonary valve.

abscess or tumor of the brain, and the neurologic department localized the lesion in the frontal lobe. The patient died after two days in the hospital.

Necropsy performed within four hours after death showed, besides the peculiar condition of the heart, two abscesses in the right frontal lobe of the brain, right internal hydrocephalus, acute splenic tumor, cloudy swelling of the liver and kidneys and a slightly enlarged thymus gland. The tonsils appeared to be normal,

even under microscopic examination. The middle and internal ears and the accessory nasal sinuses were free from pathologic changes. The primary focus for the abscesses in the brain was not found.

The pericardial sac was normal and contained no fluid. The heart weighed 265 Gm. and was about the size of the patient's fist. The myocardium was pale reddish-brown and firm. In the left ventricle, it was 12 mm. thick; in the right, 3 mm. The mitral, aortic and tricuspid valves were smooth and thin and showed no abnormal condition.

The right anterior and the posterior cusps of the pulmonary valve were of normal appearance. On the left anterior cusp (fig. 1) there were three spherical



Fig. 2.—Section through two tumor nodules, the adjacent valve insertion and the pulmonary artery. Weigert's stain for elastic tissue;  $\times 10$ .

bodies, 4 by 4 by 2 mm., 7 by 6 by 4 mm. and 6 by 4 by 3 mm., and one ovoid body 10 by 5 by 4 mm.; all were attached to the ventricular aspect of the leaflet by broad bases without the intervention of pedicles. The ovoid body was attached at the junction of the valve leaflet and the ventricular endocardium and at the extreme left; the round bodies were also closer to the insertion of the cusp, leaving above them a free portion, from 3 to 4 mm. long, of normal valve tissue. The noduli arantii was normal. The surfaces of these nodules were smooth and reddish brown, with lighter orange-brown spots the size of a pin point. They

were of rubbery, elastic consistency. There were no thrombi attached to them, nor was there evidence of thrombosis elsewhere in the heart. The whole heart was fixed in Kaiserling's solution. Then a block was removed which included portions of two tumor nodules and their attachments, the cusp, the pulmonary artery and a small portion of the ventricular myocardium (fig. 2). Sections from this were stained with hemalum-eosin, van Gieson's stain and Weigert's stain for elastic fibers.

Microscopic examination of the myocardium revealed no pathologic condition with the exception of occasional fine droplets of fat near the nuclei of a few of the fibers. Sections through the tumor nodules and the valve showed the following:

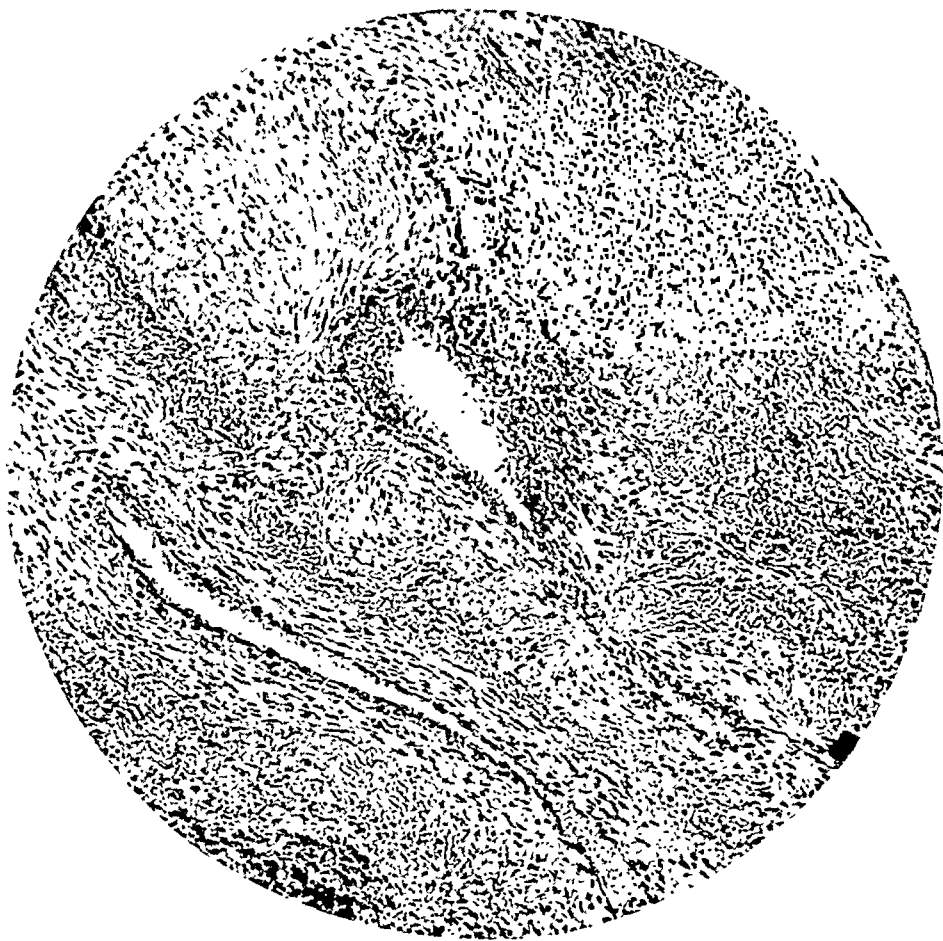


Fig. 3.—Section through the attachment of the tumor. The darker strands stained red; the lighter thick walls around the vessels stained yellow. Van Gieson stain; photographed through a green filter;  $\times 140$ .

In the elastica stain a continuous heavy band of elastic tissue passed immediately beneath the subendothelial connective tissue of the valve, downward through the junction of the tumor and the valve to the ventricle and appeared just beneath the endothelial lining of the mural endocardium. Beneath this layer the valve appeared to be normal and contained no blood vessels or cellular infiltrates. Outside of this layer there was a triangular area the base of which was composed of the elastic layer described; the apex, of the fissure between the two

nodules, and the sides, of the nodules themselves. Within this area (fig. 3) there were wide, endothelial-lined blood spaces, the thick walls of which were made up of loose concentric layers of cells which stained yellow by the van Gieson method and which had long, spindle-shaped and round nuclei. In these walls there were many concentric rings of elastic tissue, one outer ring around each vessel being more prominent than the rest. The tissue between these vessels was made up of relatively acellular connective tissue which stained red by the van Gieson method.

The tip of this triangle, at the junction of the two nodules, was rich in short, thin elastic fibers. The tumor nodules were completely enveloped by a single

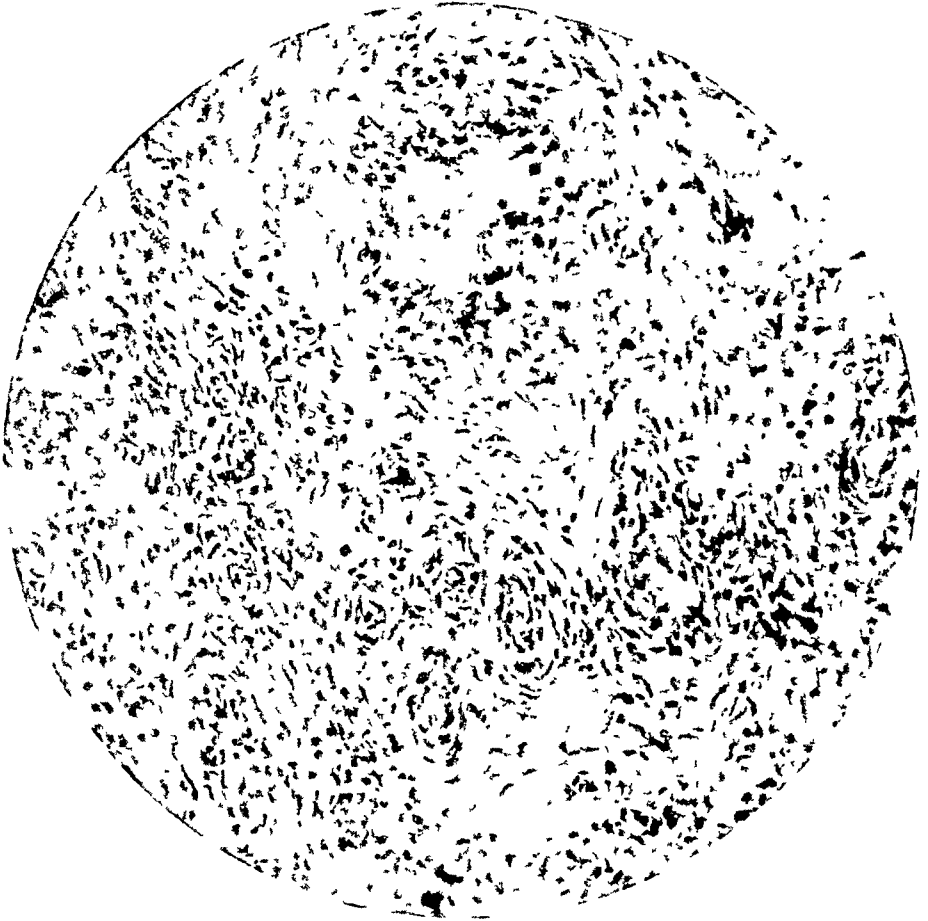


Fig. 4—Section through the interior of the tumor. Note the mantles of cells around all the small vessels. Hemalum and eosin;  $\times 300$ .

layer of flat endothelial cells. Immediately beneath this, there was a thin layer staining pink by the van Gieson method and containing long, spindle-shaped nuclei arranged parallel to the surface. The interiors of the nodules were similar and were composed of blood vessels and interstitial connective tissue (fig. 4). The blood vessels were numerous and diffusely scattered in all parts of the tumors except in the subendothelial connective tissue, in which they were entirely absent. In some places they were separated from each other by only a few cells, and made up almost all the tissue. They varied much in size, but, except for the capillaries, which were few, they all showed essentially the same structure. The

linings were prominent; the endothelium-like cells were numerous and bulged into the lumen of the vessel. Around these there appeared concentric rings of cells that stained yellow by the van Gieson stain and contained large, plump, spindle-shaped nuclei arranged concentrically around the lumen. Even the smallest vessels of capillary size contained at least two such rings of cells and the larger ones from five to eight, so that in most cases the thickness of the vessel wall exceeded that of the lumen. There was no division into layers in even the largest vessels; at most, the innermost layer was slightly more prominent than the rest. In the largest vessels, a few elastic fibers could be made out, but most of them contained no such fibers. The interstitial tissue was made up largely of long, spindle-shaped cells with thin, cigar-shaped nuclei. It was everywhere cellular; in some places it was loose, and the cells assumed a stellate appearance with long, branching processes, which gave it the appearance of myxomatous tissue. This myxomatoid tissue was especially marked near the free margin of the tumors. Clumps of golden yellowish-brown pigment were found in several places, especially near the base of the tumors. Lymphocytes in small numbers were found scattered through the attached portions of the tumors, and a few plasma cells were seen. One small accumulation of lymphocytes was found at the base of one of the tumors.

#### COMMENT

In this case there seemed to be a neoplastic process. The most striking structures were the vessels. Identical pictures were seen by Brenner<sup>8</sup> in what he called a hemangio-elastomyxoma attached to the fossa ovalis; he aptly described these vessels as consisting of a mantle of several layers of round and elongated cells, not divided into layers. Such vessels are seen in the embryo and remind one again of Ribbert's contention that these valvular tumors originate from embryonic rests within the valves. The other changes may be considered as retrogressive. Hemorrhages within benign tumors are not uncommon, and in a tumor situated on a valve which moves up and down at the rate of from sixty to eighty times a minute they are rather to be expected. The accumulation of lymphocytes and plasma cells about such liberated blood pigment is also not unusual.

It is noteworthy that in spite of the large size of the nodules and in the complete absence of portions of thrombi or definitely inflammatory tissue from which they may have arisen there should be no evidence of shrinking such as invariably occurs in the process of organization. This was emphasized by Ribbert,<sup>20</sup> who maintained that the endocardium is incapable even of organizing such large thrombotic masses. In the cases of mural tumors this is even more striking, for in a tumor filling an entire dilated auricle no contraction of scar tissue is seen. The tumors in this case, as in most others, are cellular and appear to be growing. Their apparent encapsulation by typical

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20. Ribbert, H., in Henke and Lubarsch: *Handbuch der speziellen pathologische Anatomie*, Berlin, Julius Springer, 1924, vol. 2, p. 276.



connective tissue which seems to be separate from the tumor proper is also suggestive of a neoplastic process.

In a general survey of all the cases reported it seems to me to be necessary to consider the etiology of the valvular and mural endocardial tumors together because of their similarity. In both types the great infrequency of other cardiac changes, during life and post mortem, is striking, especially in view of the frequency of both intracardiac thromboses and endocarditis as primary causes of death and as incidental necropsy observations. A rare consequence of a common chronic condition, without any signs of that condition in the greatest number of cases, is not likely to occur. The entire absence of stages intermediate between thrombi or infective vegetations and these tumors is also noteworthy. In every case either the condition is definitely a thrombus or it is a peculiar "pseudomyxoma" which the observer thinks may have been a thrombus; never does he seem to be uncertain into which class to put them. When the tumors are papillary, this character is considered, especially by Jaffé<sup>5</sup> and Ribbert, to be that of a blastomatous growth.

The suggestion of Zurhelle<sup>18</sup> that these tumors are organized blood cysts may apply in a few cases, but the same arguments against other thrombotic processes apply here as well. Koechlin's hypothesis that the valvular tumors are modified Lambl's excrescences is, I think, untenable in view of his own report of thirty-five cases of typical excrescences, all similarly situated and similarly constructed, contrasted with his three tumors which, while all different, resembled each other much more than they did the Lambl bodies.

Finally, in spite of the rarity of all tumors of the heart, secondary as well as primary, primary sarcomas originating in the endocardium do occur (Husten,<sup>15</sup> Karrenstein<sup>21</sup>), and wherever there are malignant mesenchymal tumors, benign tumors may also occur. Raw<sup>22</sup> has even described a tumor in the right auricle which microscopically resembled a soft fibroma and which had caused metastases of similar structure in the liver.

In view of these considerations, the contention of Thorel that almost none of these endocardial masses is a neoplasm cannot be entertained, and the statement of Ribbert that they are all true tumors is probably closer to the truth.<sup>23</sup>

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21. Karrenstein: Ein Fall von Fibroelastomyxom des Herzens und Kasuistisches zur Frage der Herzgeschwülste besonders der Myxome, *Virchows Arch. f. path. Anat.* **194**:127, 1908.

22. Raw, N.: *Brit. M. J.* **2**:1335, 1898.

23. Debove: *Bull. et mém. de la Soc. anat. de Paris*, 1873. Reitman: *Ztschr. f. Heilk.*, 1905, vol. 26. Djewitzki: *Virchows Arch. f. path. Anat.* **185**:14, 1906. Forel: *Internat. Clin.* **4**:147, 1919. Staffel, quoted by Kirch (footnote 16). Hagedorn: *Centralbl. f. allg. Path.* **19**:825, 1908. Simmonds: *München. med. Wehnschr.* **55**:1154, 1908. Steinhaus: *Centralbl. f. allg. Path.*, 1899, vol. 10.

## SUMMARY

A case is reported in which four distinct tumor nodules were found on the ventricular surface of a cusp of the pulmonary valve.

The tumors are considered to be true benign neoplasms, specifically hemangiofibromas.

A review of the literature indicates that most, if not all, of the tumor-like endocardial structures previously classed by some authors as pseudomyxomatous, organizing thrombi, as well as the valvular tumors, are true neoplasms.

# Laboratory Methods and Technical Notes

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## A SIMPLE INEXPENSIVE PHOTOMICROGRAPHIC APPARATUS \*

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ROCHESTER, MINN.

Some one has said, in effect, that one picture is worth a thousand words. This is particularly apropos in the respective fields of biology, in which it is often desirable to supplement a written description by photographic illustrations. Because of the large investment necessary to secure photomicrographic outfits such as are catalogued by the various manufacturers, many who might in time become proficient in this fascinating branch of photography are denied the opportunity to try their hand at it. Although photography with a hand camera is so simple that even children may secure satisfactory results, photography with the aid of a microscope is for the majority clothed in a certain amount of mystery. As a consequence, many contributors to scientific literature either resort to drawings or, perhaps, omit illustrations which frequently would constitute the most valuable part of their publications. There are others who depend on a commercial photographer or a technician to supply photomicrographic illustrations. These illustrations are not always of the highest standard of excellence, and an otherwise meritorious contribution is often relegated to mediocrity because of abominations of the photographer's art.

To secure photomicrographs of excellent quality is not difficult when a relatively simple homemade apparatus is used, nor is it necessary for the average worker to have had extensive training in photography before satisfactory results can be obtained. Of course, knowledge of practical photography is helpful and should enable one to attain satisfactory results in a shorter time than would be possible without such experience.

Once mastered, photomicrography exerts continued fascination, and as a consequence, more and better pictures are obtained for the many purposes for which photographs are required to assist in telling the story or to complete records and files. After one has experienced the satisfaction of making photomicrographs, one would be reluctant to depend on another for this work.

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\* Submitted for publication, April 12, 1929.

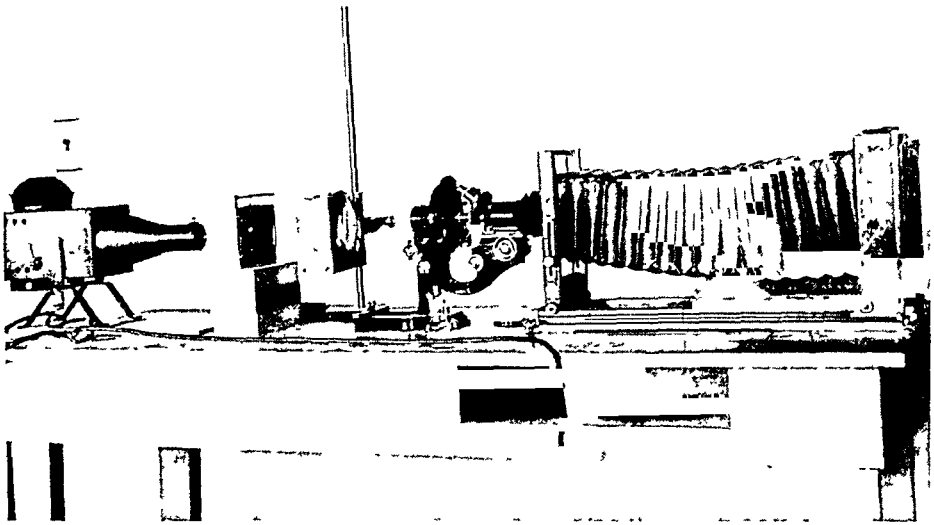
\* From the Division of Experimental Surgery and Pathology, The Mayo Foundation.

## THE APPARATUS

For nearly two years I have been making photomicrographs with an outfit which, with the exception of the microscope, was assembled from various odds and ends of laboratory equipment already available. A similar apparatus could probably be assembled at a total expenditure of \$50 or less, and the results obtainable in work as a routine are comparable with those secured by the more complicated, expensive outfits.

The respective items used to assemble the outfit consisted of a microscope, a camera with a view of 5 to 7 inches, from which the lens and shutter were removed, two planoconvex condenser lenses suspended on a ring stand, a flat museum jar 5 by 4 by 0.75 inches to hold the liquid filter and a high power mazda microscopic lamp.

The apparatus should be assembled on a rigid table of such height as to render its manipulation convenient. The table should be approximately 24 inches wide and 5 feet and 6 inches long. The camera is first firmly attached to a one-half inch



The assembled outfit; the relative positions of the respective parts of the apparatus are shown.

pine board which will elevate it sufficiently to permit the operation of the pinion which controls the movement of the bellows forward and backward. By the use of "U" clamps, and bolts with wing nuts, the base of the camera is attached at one end of the table in the middle line. The microscope is mounted directly in front of the camera, the front portion of which may be adjusted to coincide with the height of the draw tube of the microscope when the instrument is in the horizontal position. If the lens and shutter are removed from the ordinary lens board, the opening is of a convenient size for the insertion of the objective of the microscope. It is not necessary that this union be tight; light can be excluded satisfactorily by wrapping a piece of black cloth around the draw tube just in front of the lens board. The microscope is held in place by a bolt which passes through the top of the table and through a piece of steel about 5 inches long and one fourth of an inch thick which is laid across both arms of the microscope stand. With a wing nut the instrument can be readily adjusted or removed if desired. At the other end of the table, at an approximate distance of 30 inches from the substage condensing lens of the microscope, the source of light should

be placed. I have had best success with a 400 watt, 110 volt mazda lamp, such as is available for dark-field illumination or other microscopic work. The style shown in the accompanying figure can be highly recommended. It is important that the camera, the microscope and the source of light be so adjusted as to be on the same plane and in exact alinement. Much adjusting is often necessary in order to achieve this result. At an approximate distance of 18 inches in front of the lamp the glass receptacle containing the ray filter should be placed. Although the base on which this rests should be rigid, the glass cell containing the filter should not be attached thereon, since it is important that this part of the equipment be readily removed while the adjustments preliminary to exposures are being made. Between the color filter and the microscope, two condensing lenses should be mounted as shown in the accompanying figure. The source of light should be controlled by a hand switch which obviates the necessity of a shutter in making exposures. After the equipment is assembled the light should be turned on and an attempt made to center an intense point of light from the condensing lens on the closed diaphragm of the microscope. In order to secure maximal illumination evenly over the exposed field it is imperative that all parts of the instrument be in perfect alinement, and this can be obtained only by careful preliminary adjustments.

When in use it is important that the apparatus be placed in a room free from vibrations of the floor. A basement room, with a concrete floor, serves admirably.

One of the most important features of this apparatus is the evenness of the source of light compared with the type of equipment in which the less constant, although more intense, arc light is used. After experience with both types of lights, it is my opinion that for average work as a routine the incandescent lamp operated on the ordinary A-C current is much to be preferred. Although the exposures are necessarily much longer when the incandescent bulb is used, the results obtained more than compensate for the added time required.

#### SUMMARY

A simple inexpensive photographic apparatus, which may be assembled from various items of equipment that are available in a laboratory and that may have been secured for other purposes, is described.

## General Review

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### RECENT WORK ON THE EFFECTS OF INANITION AND MALNUTRITION ON GROWTH AND STRUCTURE

C. M. JACKSON, M.D.  
MINNEAPOLIS .

*(Continued from page 1078)*

#### EFFECTS OF A DEFICIENCY OF VITAMINS

First may be mentioned certain papers dealing with the effects of a deficiency of vitamins in general, either of a multiple shortage of the vitamins or of a shortage of vitamins complicated by a deficiency in other dietary factors.

Suzuki (1924) concluded that nephritis (or nephrosis) in the rabbit or in man may be caused either by infection or by toxic products arising from a disturbance of the intermediary metabolism through a deficiency of vitamins (or of similar substances). The principle of metabolic toxins was held to apply also to many other disorders, such as rickets, acute atrophy of the liver, pernicious anemia, Banti's disease and the leukemias. Abels (1924, 1925) pointed out that in avitaminosis (especially that due to a deficiency of vitamins B and C) the symptoms result from (a) dystrophy, or structural changes in the tissues; and (b) dysergy or lack of resistance of the tissues to infections. According to Cramer and Kingsbury (1924), a deficiency in vitamin A does not markedly affect the general humoral defenses of the body, but predisposes to infection through lesions in the local defenses, especially in the mucosae of the conjunctiva and of the respiratory and intestinal tracts. The importance of a deficiency of vitamins in reducing the resistance to infections was also recognized by Mellanby (1926), Eicholz and Kreitmaier (1928), Sherman and Burtis (1928) and many other investigators. The reason why a deficiency of vitamins (like inanition in general) reduces the resistance to infection is not entirely clear. Presumably the vitality of the cells and the tissues of the host is reduced relatively more than the vitality of the parasitic organisms. This theory is in agreement with observations indicating that the vitamin requirements for bacterial growth are somewhat different from those for the growth of the higher animals. The recent literature on this topic was reviewed by Uyei (1927).

Heaton (1926) showed by tissue cultures of chick embryos that the requirement for "growth hormones" or vitamins varies greatly among

the various tissues. In a solution of yeast, the cell growth of heart muscle was inhibited, while that of skin and intestine was not. The substance in yeast which promoted the epithelial growth was apparently the antineuritic vitamin B.

Since vitamins are essential to the normal growth of tissues, an imbalance or deficiency of vitamins may produce various abnormalities. Jorstad (1925) showed that the reaction of the subcutaneous connective tissue cells to coal tar in the white rat was modified by the presence or absence of vitamins A and B. The work of Fujimaki and Saiki in relation to carcinoma will be reviewed later in the discussion of vitamin A. Ludwig (1926) found that an inoculation of carcinoma usually failed in mice and rats on a vitamin-free diet, whereas it succeeded in normally fed controls. Erdmann, Haagen and Börnstein (1927) did not observe any visceral cancer in rats on diets with a low content of vitamin (similar to those used by Saiki); but they found two cases of subcutaneous adenocarcinoma (of mammary origin?) appearing in them. The authors believed that a deficiency of vitamins affects especially the reticulo-endothelial system. Erdmann and Haagen (1928) concluded that diets unbalanced in respect to vitamins favor the origin and development of tumors in rats.

Peller and Bass (1924) found the average weight of the human new-born less in the winter than in the summer. This they ascribed to a deficiency of vitamins in the maternal diet during the winter. Abels (1926) claimed that for the same reason the average weight of the new-born in Vienna was decreased during the winter after the war. Most authors, however, do not find a significant decrease in the average birth-weight during the famine that was imposed by the war.

Glanzmann (1923) fed young rats for long periods on a vitamin-free diet of casein, starch, sugar, agar and salts. Growth was retarded, and finally a loss in weight occurred with marked atrophy of the liver and lymphoid tissues. The most striking change found in cell structure was an extensive nuclear pyknosis, which was ascribed to a disturbance in the colloidal conditions of the cell protoplasm. (In this connection Guggisberg's results, commented on in this paper under the head of deficiency of vitamin A, may also be referred to.) In rats on a similar vitamin-free diet, Stammers (1926) found marked loss in weight. Hypertrophy of the suprarenal glands was absent and little, if any, decrease occurred in the lipoid content of the cortex.

Henriksen (1925, 1925a) fed rats and guinea-pigs on a diet of oats and water (deficient in protein and salts, as well as in vitamins). He found extensive cell atrophy and degeneration in the liver, spleen, kidneys and suprarenal glands, as well as in the muscle and nervous tissues. The deficiency of vitamins, according to Henriksen, affects primarily the cell nuclei, probably through their component of bound fat. Spadolini

(1923) described an atrophic degeneration of the parathyroids in cats fed an avitaminic diet of autoclaved meat.

Banu and Heresco (1925) studied the effects of a multiple deficiency of vitamins on growth and bone structure in puppies. Junkersdorf and Jonen (1925) found serious retardation of development in puppies fed with a flour gruel that was deficient in protein as well as in vitamins. A peculiar disappearance of the pigment in the ball of the foot was noted. Groebels (1923) likewise observed depigmentation in frog tadpoles (*Rana temporaria*) on a vitamin-free diet. Kopeć (1927) studied the effect of vitamin variation in the development of the moth, *Lymantria dispar*.

That there is some undetermined dietary factor essential for the utilization of fat by the body was indicated by the work of Richardson (1925). She noted that when young rats were fed on certain apparently normal and balanced diets of highly purified foods, with the addition of the known vitamins, there was, nevertheless, in some cases a failure of growth with the frequent occurrence of greasy skin and hair.

General reviews of the results of previous work on the various vitamin deficiencies were given by McCollum and Simmonds (1925), Williams, McCarrison, Cramer and Findlay (1925), Doyle (1925a), Berg (1927), Stepp and György (1927) and Plimmer (1928). Parrino and Lepanto (1925) compared the effects (especially the changes in the blood) of simple inanition and of a deficiency of vitamins in pigeons and guinea-pigs. The relationship of a deficiency of vitamins to pediatrics was discussed by Reyher (1925). The anemia and urolithiasis produced by McCarrison (1927a, 1927b) with a variously deficient diet will be mentioned later.

*Effects of a Deficiency of Vitamin A (Antixerotic).*—Recent work confirms previous conclusions that deficiency of vitamin A prevents growth and development in the young and lowers resistance to infections (Cramer and Kingsbury, 1924; Sherman and MacLeod, 1924; 1925; Sherman and Burtis, 1928; Green and Mellanby, 1928). These infections are not specific for the ophthalmic tract as was formerly believed, but (as discovered by Mori) they involve also various other organs and systems. (The results reported by Bloch in 1924 may be brought into comparison here.) The local conditions in the corneal region (desiccation due to decreased lacrimal secretion) can scarcely account for the lesions in other organs. In many regions, a peculiar dystrophy of the epithelial cells appears, with a tendency to xerosis or hyperkeratosis, and possibly also malignant changes, as will be shown later.

The calf must now be added to the list of animals for which vitamin A is indispensable, as shown by Jones, Eckles and Palmer (1926). The typical symptoms of a deficiency of vitamin A appear in this species,



including the failure to grow, xerophthalmia, respiratory troubles, diarrhea and death. Recovery is possible on the addition of cod liver oil to the diet. Beard (1926) found that vitamin A is likewise necessary for the normal growth of the white mouse; but that the xerophthalmia does not appear to be characteristic for this species. According to Wolbach and Howe (1928), the ocular changes in the guinea-pig are also comparatively slight.

The effects of a deficiency of vitamin A will be grouped for convenience under the head of the various organs involved. The earlier literature on this subject was reviewed in my former work (Jackson, 1925).

**Visual Apparatus:** In young rabbits fed "bean curd dregs," Okamoto (1925) observed the development of rickets (due to a deficiency of vitamin D), and at a later period the typical symptoms of xerophthalmia, with corneal ulceration and perforation in extreme cases.

The experimental study of the characteristic ophthalmic disorder has been done chiefly on rats. Osborne, Mendel and Cannon (1924) noted ophthalmia appearing in about 60 per cent of 493 albino rats that for twenty days or more were on diets containing little, if any, vitamin A. Cases in which the ophthalmia failed to appear (likewise the negative results of Heijinian) were ascribed to a variation in the body's storage of the vitamin, or in the amount remaining in the incompletely purified diets. The age factor was emphasized by Sherman and Storms (1925). They found that the characteristic ophthalmia before death developed in three fourths of the rats placed at the age of 1 month on a diet deficient in vitamin A, but in only one fourth of those placed on the same diet at from 2 to 9 months of age. Mori (1922) described atrophic and degenerative changes in the epithelium of the lacrimal gland, associated with deficient lacrimal secretion and resulting in desiccation and keratomalacia. In the meibomian ducts, xerosis was observed, which sometimes caused occlusion and retention cysts. The lesions in the salivary glands and in the respiratory tract will be mentioned later.

Yudkin (1924, 1926) also made a careful histologic study of the visual apparatus at various stages of the typical disorder in young white rats. His results tend to confirm the theory that the condition of the eye is due primarily to the altered secretion of the paraocular glands, permitting bacterial infection. The disturbance appears more rapid and severe when the diet lacks another factor (such as phosphorus) in addition to vitamin A. Findlay (1925) found a decrease in the lysozyme content of the tears, which would increase the tendency of the eyes to infection during the deficiency of vitamin A.

A thorough study of the various organs of young albino rats on a diet deficient in vitamin A by Wolbach and Howe (1925a, 1925c, 1925d) revealed a characteristic involvement of the epithelial tissues far more

widespread than was observed by Mori. The glandular epithelium of the body in general underwent atrophy. In many regions, including the gland-ducts and mucous surfaces of the ocular, respiratory, alimentary and genito-urinary tracts, the epithelium presented focal proliferation with a pronounced tendency to keratinization in the superficial cells. Sometimes cysts and abscesses occurred. "In a few of our animals the behavior of the replacing epithelium in respect to numbers of mitotic figures and response on the part of the connective tissue and blood vessels suggests the acquisition of neoplastic properties. While the epitheliums which are the seats of these changes are largely of covering types, glandular epithelium is involved, specifically in the paraocular and salivary glands." Significant changes in the mitochondria were not found. The study of the visual apparatus included the eye, conjunctiva, cornea and glands (lacrimal, harderian, meibomian). The other organs will be mentioned later. Wolbach and Howe also studied the tissues from the fatal case in man reported by Wilson and DuBois (to be mentioned later). They found widespread keratinization similar to that occurring in the rat. The process of keratinization in the guinea-pig was also described in detail by Wolbach and Howe (1928).

The results reported by Mori and by Wolbach and Howe were confirmed by Manville (1925) and Freudenthal (1927, 1928) in experiments on rats. Manville concluded that the primary effect of a deficiency of vitamin A is a generalized decrease in glandular activity, resulting in xerosis of the eye and other regions (mouth, salivary glands, respiratory tract, skin), making possible a secondary bacterial invasion in these regions. Frontali (1926) also noted retarded growth and typical keratomalacia, together with infections of the urinary tract (to be mentioned later).

In rats subjected to diets deficient in vitamin A, Holm (1925) noted certain symptoms (enophthalmos, loss of hair at the ciliary edges, peculiar, reddish brown secretion) not appearing in human beings with the same disease. In individual rats much exposed to light, hemeralopia (day-blindness) could be demonstrated, as in man. This condition is perhaps to be explained by the further work of Fridericia and Holm (1925). They found that the visual purple was not affected by vitamin A starvation in darkness; but when the retina had been bleached by exposure to light, the regeneration of the visual purple was delayed in the test rats. This abnormality appeared much more pronounced in the albinos than in the pigmented (pied) rats, on account of the retinal pigment in the latter.

The results of recent studies of the effects of a deficiency of vitamin A in the human species are in close agreement with the results of the experiments on animals. Wilson and DuBois (1923) reported a detailed necropsy in a fatal case of keratomalacia in an infant fed for

three months on a dilution of condensed milk. A corneal ulcer had perforated nineteen days before death. The histologic results included inflammatory changes in the pancreas and in the lacrimal and salivary glands, and keratinization of the epithelium of the trachea, bronchi, uterine mucosa and pancreatic and submaxillary ducts. The desquamation of keratinized epithelium resulted in pancreatic cysts and bronchiectases. The ophthalmic changes were characteristic, as they were also in four cases reported by Wagner (1924) and one by Schwartz (1925).

Guiral (1924) described the symptoms in about sixty cases of keratomalacia in Cuban infants fed on milk from which the cream had been removed. There were conjunctivitis and deficient lacrimation. The cornea was sometimes apparently destroyed without visible pus or other bacterial complications. The feeding of orange juice caused a rapid recovery. Stransky (1924) presented six cases in infants, and Adamantiadis (1925) five cases of varied severity in malnourished children. Bloch (1924) described the ophthalmic lesions occurring in Danish children. Widmark (1924) reached similar conclusions, based chiefly on the work of the Danish ophthalmologist, Blegvad. According to this work, xerophthalmia is to be considered as, essentially, a general disturbance of nutrition, with a loss of resistance to infections. The disorder of the eye is only a partial symptom, appearing rather late. Corneal perforation may occur, resulting in blindness. In adults, the disorder is usually arrested at an early stage, associated with hemeralopia (meaning night-blindness; usually designated as nyctalopia). Abels (1927) stated that women are less susceptible to hemeralopia, on account of the greater amount of body fat with which the storage of vitamin is associated.

Harman (1925) described the disorder known as phlyctenular conjunctivitis, which among London school children ranks next to ophthalmia neonatorum as a cause of blindness from superficial inflammation. He concluded that the chief cause is malnutrition, but does not mention the possible relationship of this disorder to a deficiency of vitamin A.

By feeding the mothers on a modification of McCollum's rachitic diet (a mixture of corn meal, white flour, wheat bran, gelatin, calcium chloride and sodium chloride), von Szily and Eckstein (1923) produced, they said, cataract in the eyes of the nursing white rats. The rats were retarded in growth but did not show signs of rickets. In addition to being deficient in vitamin A (which was considered the most important), the diet was also lacking in fat and phosphorus. Stepp and Friedenwald (1924) and Stepp (1925) were unable to confirm this result, but von Szily and Eckstein (1925) ascribed this failure to the use of a different diet. They confirmed their original result by new experiments, and suggested the possibility of a new "anticataract vita-

min Z." Jess (1925), however, not only failed to confirm the results of von Szily and Eckstein, but found cataract occurring spontaneously to a variable degree in about one third of 150 white rats examined. It appeared to be hereditary in some families. This observation threw great doubt on the whole question of experimental cataract, which awaits further investigation.

**Respiratory Tract:** Among the effects of a deficiency of vitamin A in rats, Mori (1922) observed cornification of the laryngeal epithelium, which became thickened and infiltrated with pus cells. The xerosis gradually involved the trachea and became complicated by an inflammatory condition of the trachea and lungs, which in some cases terminated in bronchopneumonia. Sherman and MacLeod (1924, 1925) also emphasized the increased susceptibility to infection and especially the tendency to diseases of the lungs appearing in young adult rats. Manville (1925) mentioned the occurrence of xerosis in the larynx, and of pyogenic infections in the nasal sinuses, the middle ear and the lungs. Wolbach and Howe (1925a, 1925c, 1925d) found the process of hyperkeratosis, with transformation of various epithelia into the stratified squamous form, "practically constant in the upper respiratory tract, including the whole of the nasal passages, larynx, trachea and bronchi." The lungs show secondary changes, due chiefly to occlusion of the bronchi with desquamated keratinized cells, i.e., bronchiectases, with or without infection. They later (1928) described similar changes in guinea-pigs on diets deficient in vitamin A. Similar results were obtained in rats by Goldblatt and Benischek (1927). Respiratory troubles were mentioned also by Jones, Eckles and Palmer (1926) as one of the symptoms of a deficiency of vitamin A in calves.

**Alimentary Tract:** Gastro-intestinal disorders are common in many forms of malnutrition, including that due to a deficiency of vitamin A. Cramer (1923) held that one specific function of vitamin A is to maintain the integrity of the intestinal mucosa, thus preventing bacterial invasion. Guiral (1924) observed that infants on a diet of skimmed milk are likely to develop diarrhea in addition to keratomalacia. A watery diet is contra-indicated, because the associated deficiency in all vitamins intensifies the disorder. Diarrhea is also mentioned as one of the symptoms of a deficiency of vitamin A in young rabbits (Okamoto) and in calves (Jones, Eckles and Palmer).

Mori (1922) found normal cornification in the oral mucosa of rats on diets deficient in vitamin A. The salivary glands (parotid, submaxillary and sublingual), however, showed atrophic epithelium with deficient secretion. The epithelium of the salivary ducts often presented a remarkable degree of cornification and desquamation, occluding the lumen so as to form retention cysts and abscesses. Manville (1925) mentioned xerosis of the mouth, with oral, lingual and salivary

abscesses. Sherman and Munsell (1925) noted pus in one or more of the glands at the base of the tongue in 76 per cent of the cases. Wolbach and Howe (1925a, 1925c, 1925d) found the specific keratosis appearing in the salivary and accessory glands of the mouth and pharynx, and more rarely in the pancreas (especially in the ducts). Abscess-like cavities may occur, with yellowish, cheesy content from desquamated, keratinized epithelium. Goldblatt and Benischek (1927) observed similar lesions and emphasized especially the occurrence of abscesses at the base of the tongue. Fujimaki and others (1927) did not find any definite changes in the epithelium of the esophagus in test rats.

Lesions of the teeth were observed in albino rats deficient in vitamin A by Jackson (1925a). The incisor teeth appeared chalky-white, irregular and sometimes broken. The upper incisors were sometimes greatly elongated, failing to articulate with the lower. Wolbach and Howe (1925d) noted but few gross changes in the teeth of their test rats, although there was a variable atrophy of the odontoblasts and an irregular formation of dentine. Marshall (1927) observed attrition and abrasion of the tooth surface in both the test rats and the normal controls. Caries appeared in the adult test rats, but not in the younger ones. Lesions of the pulp, such as abscesses and calcification, were demonstrable in teeth that did not show caries as well as in those with caries. Although caries was apparently produced by the deficiency of vitamin A, it was not altered or arrested by a later addition of vitamin A to the diet.

Although Wolbach and Howe did not find any changes in the epithelial lining of the stomach and the intestines, they mentioned that the proliferative changes in other regions suggested the acquisition of neoplastic properties. Pappenheimer and Larimore (1923) observed gastric lesions in twenty of thirty-six rats on diets variously deficient. The addition of cod liver oil to a diet deficient in a fat-soluble vitamin afforded complete protection. Lesions were not found in forty-three rats on adequate diet. The lesions included an inflammatory edema of the mucosa and the submucosa, with a marked cellular reaction and localized ulceration. They occurred near the ridge at the junction of the fore-stomach and the glandular stomach. In a later study (1924), the gastric lesions were found in sixty-eight (61 per cent) of 112 rats on deficient diets, and in only five (7 per cent) of sixty-six controls; but an irritation by ingested hairs was thought to have been an important pathogenic factor.

Reference was made in a previous paragraph to the epithelial changes produced by Fujimaki and his associates (1927, 1927a) (Saiki 1927). The vitamin A deficient diet of casein, dextrin, olive oil, salt mixture and yeast was fed to young or adult rats for periods varying

from 58 to 318 days. The location and frequency of the most definite epithelial changes produced were summarized as follows:

TABLE 1.—*The Epithelial Changes Caused in Rats by a Diet Deficient in Vitamin A (as Observed by Fujimaki and His Co-Workers)*

Organs in Which Lesions Occurred	Number of Rats	Degrees of Hyperkeratosis and Atypical Epithelial Growth with Incidence of Each		
		Marked	Moderate	Slight or Absent
Fore-stomach.....	49	5 (10%)	12 (24%)	32 (66%)
Sublingual duct.....	29	7 (24%)	9 (31%)	13 (35%)
Bladder.....	30	3 (10%)	4 (13%)	23 (77%)
Renal pelvis.....	39	2 ( 5%)	2 ( 5%)	35 (90%)

Definite gastric changes thus appeared in about one third of the rats tested. The occurrence of papillomatous or carcinomatous lesions in the rats on diets deficient in vitamin A was previously reported by Fujimaki at meetings of the Japanese Pathological Society and the Fourth Congress of the Far Eastern Association of Tropical Medicine in 1925. The proliferative changes in the stomach apparently began with hyperkeratosis and epithelial growth unassociated with any local inflammatory reaction or preliminary ulceration. Along with the development of a heterotopic invasion of proliferated epithelia, a round cell infiltration in the mucosa and submucosa gradually became more distinct. The characteristic changes were not found in the cylindric epithelium of the glandular portion of the stomach, bile duct, uterus, trachea or bronchi. However, in one case a metastatic formation appeared in the lungs. The more negative results of Erdmann and her associates on diets of similarly low vitamin content were mentioned in a previous paragraph.

Possibly because the liver is normally rich in stored vitamin A (as shown by Wagner in 1924, and others), few observers have noted any results of a dietary deficiency of vitamin A in this organ, aside from moderate atrophy of the gland cells. Mori, Wolbach and Howe did not find any specific changes in the liver. Fujimaki (1926) and Saiki (1927), however, were able to produce biliary as well as urinary calculi. The concretions appeared in the bile ducts (the rat not having a gallbladder), and developed more readily when the diet was deficient in protein or phosphorus and calcium as well as in vitamin A.

Urinary System: The effects of a deficiency of vitamin A on the urinary system have been frequently demonstrated. Mori (1922), however, did not find any abnormality in the kidneys. One of the most significant and important of recent advances was the experimental production of lesions of the urinary tract, with formation of calculi, by means of the deficient diet.

An epidemic of nephritis was observed by Jackson (1925a) in a colony of albino rats fed on a cereal mixture apparently deficient in

vitamin A. The kidneys showed various stages of a focal interstitial nephritis, with round cell infiltrations. Some of the tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was ascribed to an infection made possible by the lowered resistance. When one nephritic kidney was removed, the other usually showed marked and progressive compensatory hypertrophy (up to 120 per cent), with a simultaneous decrease in body weight.

In seven young white rats that had died with xerophthalmia on diets deficient in vitamin A, Frontali (1926) likewise found constant infections of the urinary tract. Six of the seven showed multiple renal abscesses, either gross or microscopic, and the seventh had renal congestion and hemorrhages. The renal pelvis and ureter were also involved. All seven showed a variable degree of cystitis with sub-mucous infiltration, epithelial desquamation, metaplasia of epidermic type and formation of corneous pearls.

In rats and guinea-pigs deficient in vitamin A Wolbach and Howe (1925a, 1925c, 1925d, 1928) likewise observed the characteristic epithelial keratosis in the renal pelvis, the bladder and the seminal vesicles, but not in the renal parenchyma. Fujimaki, Kimura, Wada and Shimada (1927, 1927a) (the results reported by Saiki in 1927 may also be consulted) similarly found hyperkeratosis and atypical epithelial proliferation in rats suffering from a chronic deficiency of vitamin A. As shown in the preceding paragraphs, the lesions were most distinct in the stomach and the sublingual duct, but in a smaller percentage of cases appeared also in the urinary bladder and the renal pelvis. Other epithelia showed little, if any, change.

Fujimaki (1926) and Saiki (1927) also investigated the occurrence of calculi in the urinary tract and the bile ducts in hundreds of albino rats on diets variously deficient. The concretions appeared sooner in the rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In six rats stone in the bladder (shown by x-rays) disappeared after the animals had been placed on a diet rich in vitamin A.

The experimental production of stone in the bladder (urolithiasis) was also accomplished by McCarrison (1927a, 1927b, 1927c, 1928), using an unbalanced cereal or flour diet (deficient in protein as well as in vitamin A and probably D), with or without excess of earthy phosphates. Of seventy-two young rats on the test diet for more than eight weeks, twenty-one (or 30 per cent) had stone in the bladder post mortem. The stones were small and single or multiple (up to five), and were mainly composed of earthy phosphates. Eighteen of the twenty-one with stone showed also variable degrees of cystitis, and in eight cases one ureter was distended with pyonephrosis or hydro-

nephrosis. Stones were not found in 340 normal rats on the stock diet. The addition of milk to the cereal diet invariably prevented the formation of the calculi.

Van Leersum (1927, 1927a, 1928, 1928a) also produced phosphatic calculi, sometimes demonstrable by x-rays, in the ureter and urinary bladder in rats on standard diets deficient in vitamin A. Of 645 test rats, 197 (35.4 per cent) had calculi; forty-six showed, in addition, hematuria. Calculosis was found much more frequently in the male than in the female rats. Cystitis was not observed. In 88 per cent of the test animals examined, sections of the kidney showed also numerous small calcareo-fatty granular concretions or casts in the tubules and ducts. He believed that morbid changes in the epithelium of the renal tubules caused the calcareous deposits, and that these became liberated and grew to form larger concretions in the bladder. Perlmann and Weber (1928) similarly obtained bladder stones in rats. Hughes (1928), however, did not find urinary or biliary calculi resulting from a deficiency of vitamin A in hogs; but in chickens he observed heavy deposits of urates throughout the body.

Blood: Cramer's theory (1923) that the blood platelets are reduced in number by a deficiency of vitamin A has not been confirmed by more recent work. Stammers (1925) did not find any significant change in the platelet count. Falconer and Peachy obtained an average reduction of 204,209 in twenty-four platelet counts on test rats, but concluded that the change was not sufficiently striking or constant to be held specific. They also found a slight increase in the number of red cells; and some leukocytosis with an inversion of the polymorphonuclear-lymphocyte ratio, which they ascribed to the frequent presence of low grade infections. In a case of keratomalacia in an infant Schwartz (1925) made a blood count of 4,800,000 red cells, and 13,500 leukocytes (78 per cent of which were polymorphonuclears and 22 per cent lymphocytes).

As a result of extensive dietary experiments on white rats, Koessler, Maurer and Loughlin (1926) concluded that vitamin A is necessary for the normal regeneration of blood, and that its absence produces a condition similar to pernicious anemia. McCarrison (1927a, 1927b) similarly found (in addition to urolithiasis) a condition resembling pernicious anemia in rats on defective diets, deficient in protein as well as in vitamin A.

Reproductive Tract: In many of the studies to be mentioned here, a deficiency of vitamin E (mostly unrecognized) probably complicated the effects of the deficiency of vitamin A. Yamasaki (1923) fed sixty adult white mice a basal ration of casein and polished rice, plus additions to make a normal (complete) diet in one group and variously deficient diets in other groups as follows: group 1, a diet deficient in salt; group



2, a diet deficient in vitamin A; group 3, a diet deficient in vitamins B and C; group 4, a vitamin-free diet; and group 5, a diet of water only. Some died on the deficient diets; others were killed in three weeks. In all the test groups, characteristic changes appeared in the gonads—a disturbance of spermatogenesis in the testis and follicular atrophy in the ovary. The ovary in some individual cases showed an apparent increase in the stroma and the interstitial gland cells. The testis presented a variable amount of degeneration in the seminiferous epithelium, but with little change in the interstitial gland cells. Giant cells appeared in the seminiferous tubules in all the test groups excepting those on water only. In general, the changes were greatest in the mice dying after the longest periods. Those in group 2 (on the diet deficient in vitamin A) showed gonadal changes similar to the changes observed in group 3; somewhat more extensive than the changes found in group 1, but less than those observed in groups 4 and 5.

The remaining studies were chiefly on the rat (the species unfortunately was not stated in some cases). Sherman and MacLeod (1925) fed rats on a diet containing too little of vitamin A, which permitted growth to nearly average adult size, but usually resulted in sterility. Parkes and Drummond (1926) found that rats on a diet deficient in vitamin A were dwarfed, weighing from 70 to 90 Gm. at from three to five months, and were sterile. Histologic examination did not reveal any reason for this sterility. "Gametogenesis was found to be in progress in these stunted animals, and the accessory organs appeared to be normal." Vaginal smears showed estrual cycles in the females. Since the test rats failed to copulate with each other or with normal rats, it was concluded that their sterility was due primarily to physiologic debility. With recovery of normal weight by the rats, on natural diets, breeding and fertility were restored. Stone (1925), on the contrary, did not find any significant decrease in the copulative ability of male rats on diets deficient in vitamins A and B; but these rats were apparently less severely stunted in growth. They showed, nevertheless, a retardation in spermatogenesis and in the development of the accessory reproductive apparatus.

Guggisberg (1925) fed rats from the eighteenth day of age on Glanzmann's diets, vitamin-free or deficient in vitamin A. Growth was greatly retarded for from seventy to ninety days, with imperfect development of most of the organs, especially of the reproductive tract. The ovaries were small, with immature follicles; the uterus small with thin walls. The testes also were hypoplastic. Spermatozoa were rarely matured, although the interstitial cells were well developed. Pregnancies (which were rare) usually resulted in abortion or weakly developed young. In general, the effects on the testis were much greater than those on the ovary. Likewise, the results of a vitamin-free diet were more marked than those of a diet deficient in vitamin A alone.

Simonnet (1925) likewise found a difference between the sexes in the effects of a deficiency of vitamin A on the gonads of rats. With retarded general growth, the weights of the testis were markedly subnormal, while the weights of the ovary appeared more nearly normal. The atrophy of the testis was also much greater than that resulting from simple underfeeding. The rats on diets deficient in vitamin A were sterile, but fecundity was restored on refeeding with a complete diet. The possibility of an antisterility vitamin E was recognized. Goldblatt and Benischek (1927) also mentioned atrophy and degeneration of the epithelium in the tubules of the testis.

According to Fujimaki and his associates (1927), the epithelial hyperkeratosis characteristic of a deficiency of vitamin A is slight or absent in the uterus and vagina of the rat. Wolbach and Howe (1925d), on the contrary, noted the occurrence of keratinization in the uterus and oviducts, as well as in the epididymis, prostate and seminal vesicles of the rat. The process began in the uterine glands as well as in the uterine lining epithelium, which became stratified and keratinized. They (1928) found the keratinization of the uterine epithelium much greater in the guinea-pig than in the rat.

As Light (1927) pointed out, this characteristic keratosis of the epithelium (rather than any ovarian disturbance) probably caused the typical continuous appearance of cornified epithelial cells in the vaginal smears of female rats on diets deficient in vitamin A. Evans (1928) noted that although estrum and ovulation may continue in rats on a diet deficient in vitamin A, only one fifth of the copulations lead to the birth of litters. The cornified cells in the vaginal smears continue throughout gestation. Bishop, Scott and Morgan (1928) observed multiple uterine deciduomas occurring in a rat on a diet containing too little vitamin A.

Suprarenal Gland: Plaut (1923) confirmed the occurrence of a hypertrophy of the suprarenal glands in avitaminosis. In four control rats, the suprarenal glands formed 0.25 per cent of the weight; in four on diets lacking in vitamin A, the suprarenal glands contributed 0.4 per cent of the weight; in four on a diet deficient in vitamin B, the glands totaled 0.6 per cent, and in two on a diet deficient in all the vitamins, the suprarenal glands made up 0.8 per cent. Hemorrhages were not noted in either the cortex or the medulla. Wolbach and Howe (1925d) did not find any gross or histologic changes in the suprarenal glands of rats on diets lacking in vitamin A. In young rabbits, with experimental xerophthalmia, Okamoto (1925) noted enlargement of the suprarenal glands, with thickening of the cortex. Kolliner (1927) observed the nucleus-plasma ratio in the suprarenal cortex and medulla of rats on variously deficient diets (wheat plus various additions), but did not reach a definite conclusion as to the results.

Miscellaneous Organs: Wolbach and Howe (1925a, 1925c) noted, among other changes, a marked atrophy of the epithelial tissues in the thyroid, parathyroid and pituitary glands of rats with experimental xerophthalmia. However, they failed (1928) to find this atrophy in tests on guinea-pigs. Plaut (1923) found in rats with avitaminosis an atrophy of the parathyroids and a decrease in the fat content of the parathyroids. He also noted abundant sudanophil fat in the spleens of rats on diets lacking in vitamin A but not in those of rats on diets deficient in vitamin B. The splenic megakaryocytes disappeared, as was observed by Wolbach and Howe (1925d).

One might expect the hyperkeratosis described by Wolbach and Howe and others as a specific effect of a deficiency of vitamin A to be most definitely manifested in the epidermis. But this apparently does not occur. Manville mentioned a xerosis of the skin; but Wolbach and Howe and Fujimaki and Saiki found little, if any change (aside from atrophy). Frontali (1926) noted multiple small cutaneous abscesses in two of seven young rats with xerophthalmia from a diet deficient in vitamin A. Portman (1927) found a general atrophy of the skin (excepting the stratum corneum) in rats with a deficiency of vitamin A; similar observations were made with regard to a deficiency of vitamin B and to general underfeeding.

Hayashi (1924c) did not find any appreciable changes in the skeletal muscle and peripheral nerves of rats with a deficiency of vitamin A. This is in agreement with the results of Wolbach and Howe (1925d). Hughes and Leinhardt (1928), however, reported nervous symptoms (incoordination, spasms, blindness) in pigs on diets deficient in vitamin A. A degeneration of the peripheral nerve fibers was demonstrated. Atrophic changes in the bone-marrow and the thymus of the guinea-pig were also noted by Wolbach and Howe (1925d). In some cases, the thymic (Hassall's) corpuscles were greatly enlarged and were cyst-like, filled apparently with desquamated, keratinized cells.

The rachitic changes found by Davis (1923) in the skeletons of puppies on rations deficient in vitamin A were doubtless due chiefly to an associated deficiency of vitamin D. On the other hand, the changes observed by Pappenheimer and Dunn (1925) in the "leg weakness" of chicks on a diet of maize and skimmed milk were apparently not rachitic. The skeletal lesions—arrested osteogenesis, osteoporosis and fibromyxomatous transformation of the marrow—point rather to a deficiency of vitamin A. The disorder was prevented or cured by the addition of cod liver oil to the diet.

According to Freudenthal (1927, 1928), the changes in the region of endochondral ossification in young rats suffering from a deficiency of vitamin A include a general inhibition of the process of osteogenesis.

*Effects of a Deficiency of Vitamin B (Antineuritic).*—Evidence has been steadily accumulating that what heretofore has ordinarily been termed vitamin B is composite in nature. In addition to the well known antineuritic vitamin, there is in yeast at least one other distinct and separable component, sometimes termed the "growth promoting factor," which will be more fully discussed under the head "Recently Discovered Vitamins." However, most of the work up to the present on the effects of a deficiency of vitamin B has involved both factors, and the exact effects of the deficiency of the antineuritic vitamin alone are therefore still uncertain.

To the earlier work indicating that vitamin B (including both factors) is indispensable for growth may now be added the observations of Osborne and Mendel (1924a, 1925) Reader and Drummond (1926), Sure (1927, 1927a) and Moore, Brodie and Hope (1927) for the rat; Beard (1926) for the mouse; Utsumi (1924) for the chick, and Bechdel, Eckles and Palmer (1926) for the calf. Aron and Gralka (1925) added evidence that in growing rats vitamin B is not stored to any appreciable extent; and, according to Sure, this is especially evident when the lactating mother has been subjected to a deficiency of vitamin B. Clementi (1924) found that adult albino rats on a diet of polished rice (mixed deficiency) underwent a loss of weight, while the young showed arrested growth and nervous symptoms of the spastic-paretic type. Guest, Nelson, Parks and Fulmer (1926), Moore, Brodie and Hope (1927), Sure (1924a, 1927), Mottram (1928) and others showed that the amount of vitamin B necessary for normal lactation is much greater than that required for normal growth and reproduction in the rat. Evans and Burr (1928) demonstrated that the increased requirement during lactation is for the antineuritic rather than the "growth promoting" vitamin B factor, and that about five times the usual intake is required during the latter half of the lactating period.

Frank (1923) noted that in young rats on fatty diets rich in vitamin A, and deficient in B and C, the skin may present an eruption, similar to that in the exudative diathesis of infants. Ishido (1922) noted a delay in the healing of skin wounds in rats and guinea-pigs on diets deficient in vitamin B and vitamin C, respectively. Frog tadpoles (*Hyla septentrionalis*) on a diet of white bread (mixed deficiency) developed paralyses, muscle degeneration, cardiac dilatation, edema, joint lesions and peritoneal hemorrhages, as observed by Hoffmann (1926). In this case, as in the monkeys fed only on polished rice by Paffrath and Schlossman (1926), one may be dealing with a mixture of beriberi and scurvy. The same possibility is to be suspected in the case of hemorrhagic disorder of the new-born described by Moore and Brodie (1927). Moore, Brodie and Hope (1927), however, produced in young rats on a diet deficient in vitamin B conspicuous subcutaneous, visceral and intracranial hemorrhages (both macroscopic and micro-

scopic), in addition to the usual paralysis and degeneration of the peripheral nerves. Similarly, Sure and Schilling (1928) noted hemorrhages especially constant and conspicuous in the bones of the young rats (which were not susceptible to scurvy).

The mechanism of the pathogenesis in beriberi in man and experimental polyneuritis still remains uncertain. Ogata (1920) supported the view that the "rice disease" (polyneuritis gallinarum) is a disturbance of carbohydrate metabolism, caused by a lack of the antineuritic vitamin B. Riquier (1925) held that the disturbance involves metabolism in general and not merely that of carbohydrates, and that it results in toxic products which injure the various tissues and organs, thereby causing the characteristic phenomena of the disorder. Wetzel (1924), as did earlier observers, found the loss of weight in pigeons on a diet of polished rice similar to that in complete starvation. Drummond and Marrian (1926) likewise concluded that the failure of nutrition in rats lacking in vitamin B is essentially the same as in simple starvation. Kon and Drummond (1927), feeding the same amount of food to control pigeons as was consumed by those on diets deficient in vitamin B, did not find evidence that this vitamin controls carbohydrate metabolism. While the acute nervous symptoms appeared only with a deficiency of vitamin B, these symptoms could not be attributed to the degenerative changes in the nerves, which occurred also in the control group. Their conclusion, in agreement with that of Ogata and his co-workers (1924a), is that existing theories do not satisfactorily explain the rôle of vitamin B in the organism. Plimmer and his associates (1927) suggested that vitamin B is a constituent of the cell nucleus and is therefore involved in all cell growth and maintenance.

Graeff (1925) concluded that in beriberi in man the clinical and anatomic data indicate the primary importance of the changes in nerves and muscles (perhaps including those in the muscle of the arteries and the gastro-intestinal canal) together with the dilatation of the right side of the heart. The venous stasis following the cardiac dilatation causes the edema and secondary changes in the various organs. Yet, in experiments on animals, the nervous symptoms and changes are apparently not proportional to the deficiency of vitamin B. Graeff therefore believed that some infectious agent, as well as the deficiency of vitamin, may be a factor in the pathogenesis of beriberi.

Ogata and his associates (1921, 1923, 1924, 1924a) vigorously opposed the doctrine that beriberi in man is identical with the experimental B avitaminosis (polyneuritis avium), emphasizing the differences between the two disorders, as summarized in the accompanying table.

On the other hand, Murata (1923) concluded that the disorder in rice-fed rabbits is essentially identical with beriberi in man, in etiology,

pathology and clinical phenomena. Minor discrepancies he ascribed to the difference in species. McCarrison and Norris (1924) and McCarrison (1928) likewise concluded that the basal factor in causing beriberi in man in India is a diet deficient in vitamin B. Experiments on pigeons, however, indicated that there is also an associated unknown agent specifically affecting the heart. Hayashi's (1924a) comparison of "polished rice disease" in the rat with beriberi in man was inaccessible.

Kepler (1925) described a case of typical beriberi in a negro woman of Philadelphia. She had lived over a year on a diet consisting chiefly of raw starch. Prompt recovery followed the addition of yeast to the diet. Scott and Herrmann (1928) found many cases among the rice farmers of Louisiana. Hoobler described the symptoms of a deficiency of vitamin B in children.

TABLE 2.—*Differences Between Beriberi in Man and Experimental B Avitaminosis (Ogata)*

Points of Comparison	Beriberi in Men	Deficiency of Vitamin B in Birds
Content of vitamin B in organs	Unchanged	Decreased
Nervous symptoms.....	Appear early in disease	Appear late in disease
Pulse rate.....	Increased	Not increased; slower toward end
Cardiac hypertrophy.....	Present	Absent (heart usually contracted)
Edema.....	Always present	Occasionally present
Edema in body cavities.....	Frequent	Occasionally present
Dyspnea.....	Present (respiratory paralysis)	Absent
Digestive disturbances.....	Slight	More severe
Red cells and hemoglobin content	Changes not marked	Distinctly decreased
Lymphopenia.....	Absent (sometimes lymphocytosis)	Marked and characteristic
Hemorrhagic diathesis.....	Absent	Present
Fever.....	Slight	Absent
Suprarenal glands.....	Medulla hypertrophied; chrome reaction increased	Cortex hypertrophied; medulla normal
Gonads (testis).....	Changes not marked	Atrophy; decreased spermatogenesis
Resistance to infection.....	Sometimes dysentery and typhoid complications	Marked predisposition to septicemia and other infections

Grey (1928) concluded that in Japan the predominant rice diet results in a widespread "preberiberi" chronic condition, involving various factors as well as the deficiency of vitamin B. From experiments on pigeons, Grey (1928a) attributed the action of the vitamin B complex to two factors: a factor regulating oxidation in metabolism; and a factor maintaining the integrity of the tissues. In the absence of the latter, the tissues tend to degenerate in the following order: endothelial or epithelial, glandular, plain muscle, skeletal and nervous. Wenckebach (1928) believed that the retention of water, affecting particularly the nervous and muscular tissues, is the fundamental factor in the pathogenesis of beriberi.

Nervous System: Nearly all investigators find degenerative changes in the peripheral nervous system accompanying a deficiency of vitamin B, but they do not all agree as to the extent and significance of such



Riquier did not find any constant or important changes in the sympathetic ganglions of polyneuritic pigeons, by Nissl's or Cajal's methods, a result confirmed by Woolard for the rat. Kingery and Kingery, however, described marked degenerative changes in the sympathetic ganglion cells of the rat (Nissl's method).

The changes in the central nervous system during beriberi (polyneuritis) appear to be variable. Richter (1913) noted a marked hyperemia with extravasations and progressive degeneration of the nerve cells in pigeons. Segawa (1914) observed degeneration especially in the cells of the anterior horn of the spinal cord. Lhermitte (1916) did not find any definite change in the spinal cord in the chick, studied by the Nissl method, but marked chromatolysis and proliferation of neuroglia cells in the cortex of the brain. Kihn (1922), in addition to vacuolation and chromatolysis of the nerve cells, found congestion, edema and multiple hemorrhages of variable size in various parts of the brain in pigeons and rats. In the rabbits observed by Murata (1913), the brain appeared subnormal in weight. Kingery and Kingery (1925) described degenerative changes in Purkinje's cells in rats, but Woolard (1927) did not find any abnormality in the central nervous system. Riquier (1925) similarly concluded that in the pigeon changes in the brain cells are relatively slight and of secondary importance. According to Grey (1928a), the neural symptoms arise late during the "polished rice disease" in pigeons, and are ascribed to irritation of the nerve cells through lymph congestion or hemorrhage in the central nervous system.

**Musculature:** In polyneuritic chickens and pigeons, Segawa (1914) found degeneration of the skeletal muscle, which was considered as secondary to the lesions of the peripheral nerves. In experimental beriberi of rabbits, Murata (1923) observed gross atrophy of the muscles, especially in the hind limbs. Occasional small grayish spots showed (on microscopic examination) the so-called waxy Zenker's degeneration which occurs in beriberi in man. Atrophy of the muscle fibers appeared, with nuclear proliferation. There was also a variable interstitial fibrosis with leukocytic infiltration, and sometimes fatty metamorphosis or edema. The respiratory muscles (diaphragm, intercostals) in general were less affected than the peroneal. The degenerative lesions rarely appeared in animals dying without symptoms of beriberi. On the other hand, in beriberi in pigeons, Riquier (1925) usually found merely simple atrophy of the fibers in the muscles of limbs and trunk, these muscles being greatly reduced in volume. A few fibers showed homogeneous structure, loss of striation and doubtful nuclear proliferation. Some fibers showed rows of sudanophil droplets. Tamura (1924) found in chickens either starved or on a diet of polished rice, a great decrease in the fat content of the muscles;



but a tendency toward increase in the cholesterol content. In beriberi in man, Pons and Lalung-Bonnaire (1927) observed the successive involvement of the diaphragmatic, inferior costal, superior costal and pectoral musculature, resulting in respiratory paralysis.

**Heart and Blood Vessels:** The changes in the heart in beriberi have been much disputed. Cardiac hypertrophy (of the right ventricle) secondary to respiratory (circulatory) obstruction, has been found characteristic of beriberi in man (Aalsmeer and Wenckebach, 1928), in contrast with the cardiac atrophy usually noted in the experimental polyneuritis of animals (Ogata and his co-workers, 1923 and 1924). In some cases, cardiac distention (which frequently occurs in the atrophic hearts) was apparently confused with cardiac hypertrophy. Segawa (1914) noted dilatation of both ventricles in polyneuritic chickens and pigeons. He thought that a toxic myocardial degeneration caused the cardiac insufficiency resulting in general venous stasis. Ogata (1920) found that, even though loss in weight was prevented by forced feeding of the test chickens and pigeons, there was myocardial atrophy with a decrease in the weight of the heart. Riquier (1925) observed a weakening and distention of the heart in pigeons, although but slight degenerative changes appeared in the cardiac muscle. Shiga (1926) asserted that he had seen cardiac hypertrophy in monkeys on a diet of polished rice. McCarrison and Norris (1924) and McCarrison (1928) concluded that even in pigeons there are different types of the disorder, including polyneuritis (in the absence of vitamin B) with cardiac atrophy, and beriberi, caused by a deficiency of vitamin B, with the presence of some unknown associated factor producing cardiac hypertrophy. Plimmer and his associates (1927) mentioned a frequent cardiac enlargement in birds, especially chickens, with chronic deficiency of vitamin B.

Kure assumed that the cardiac hypertrophy in beriberi in man is the result of respiratory paralysis, and produced (according to the record) a similar effect in the rabbit by section of the phrenic nerve. In beriberi in man, however, Ukai (1920) found that the hypertrophy of the right ventricle is not always accompanied by phrenic degeneration. Murata (1923) demonstrated that in beriberi in rice-fed rabbits the weight of even the distended heart (including blood) remains nearly stationary, while that of the empty heart averages 34 per cent below normal. The separate weights of the atria and of the right and left ventricles show slight changes. Sundararajan (1928) statistically demonstrated the cardiac atrophy in McCarrison's polyneuritic pigeons.

Moore and Brodie (1927) noted hypertrophy and dilatation of the right ventricle in a case of infantile beriberi. A series of studies on beriberi in man in Cochin-China recently appeared. Bablet and his co-workers (1927) described the radioscopic appearance in the cardiac

enlargement and displacement. Death is usually caused by the cardiac or cardiorespiratory disturbance. Pons and his associates (1927) described the clinical cardiac and respiratory phenomena. The cardiac injury, according to them, is reflected in the lung; and the respiratory condition in turn reacts on the weakened heart. Bernard and others (1927) concluded that cardiac insufficiency and capillary alterations are extrarenal factors in producing the edema of beriberi in man. Hydro-pericardium is a characteristic phenomenon, both in beriberi in man (Bernard and his associates) and in experimental polyneuritis (Segawa, 1914). As has been noted, Scott and Herrmann (1928) emphasized the importance of the cardiac lesions in beriberi in man. Mebius (1928) described a primary hydropic degeneration of the cardiac muscle in beriberi in man.

A fatty degeneration of the smallest arterioles and of the capillaries, but not of the larger vessels, was observed by Alpern (1923) in the wings of pigeons on a diet of autoclaved rice. These changes were not found in complete starvation. Fatty degeneration in the media of the small arteries of polyneuritic birds was noted also by Segawa (1914). As has been mentioned, hemorrhages in beriberi have been found by various investigators.

**Stomach and Intestines:** Ogata (1920) found relatively slight changes, including atrophy and catarrh of the mucosa, in the gastro-intestinal wall of rice-fed chickens and pigeons. Nevertheless, Ogata and his associates concluded that more severe digestive disturbance is one of the diagnostic features distinguishing experimental polyneuritis of animals from beriberi in man. Moore and Brodie (1927) observed merely hyperemia of the stomach and duodenum in their case of infantile beriberi. Scott and Herrmann found the gastro-intestinal symptoms vague and inconstant. Atrophic and degenerative changes in the gastro-intestinal mucosa of cats on a diet of autoclaved meat (deficient in vitamins B and C) were noted by Spadolini (1922). Somewhat similar though relatively slight changes (chiefly secondary to the venous stasis?) were described by Murata (1923) as occurring in rabbits, and by Riquier (1925) as occurring in pigeons. Carra (1925) and Guarino (1927) found the gastro-intestinal lesions in polyneuritic pigeons similar to those in scorbutic guinea-pigs. Plimmer and his associates (1927) observed abundant abdominal fat and frequent intestinal stasis in birds (chickens, ducks, pigeons) during chronic deficiency of vitamin B. Gastric atony and distention were noted by Rowlands and Browning (1928) in rats on diets short of vitamin B. The involvement of the digestive tract is doubtless largely responsible for the general malnutrition which is so frequent in inanition due to deficiency of vitamin B and other partial dietary deficiencies, especially in the later stages.

Larimore (1928) found that chronic ulcerative colitis in man is greatly relieved by diets rich in vitamins, especially vitamin B.

Liver: Ogata (1920) noted that in voluntary feeding of chickens on polished rice there was a marked atrophy of the liver, associated with loss in body weight, which he ascribed to simple inanition; whereas during forced feeding of rice there was a striking hypertrophy of the liver (from 50 to 80 per cent), associated with fatty infiltration, although the weight of the body increased only 4.5 per cent. In pigeons, with forced feeding of rice, there was an average loss of 12 per cent in the weight of the body, with but little change in the weight of the liver. Lopez-Lomba and Randoin (1923) found a loss of from 30 to 35 per cent in the weight of the body and of 45 per cent in the weight of the liver in pigeons on a diet deficient in vitamin B. McCarrison and Norris (1924) observed enlargement of the liver in one type of *beriberi columbarum*. In rice-fed pigeons, Riquier (1925) observed marked and uniform hepatic congestion, with bile vessels also dilated, atrophy of the parenchyma, with slight amounts of fat and glycogen, and, rarely, small hemorrhages or round cell infiltration. Carra (1925) noted moderate fatty infiltration of the liver cells in *beriberi* in pigeons. In rice-fed rabbits, Murata (1923) found a marked loss in the weight of the body and that of the liver. The liver grossly appeared paler and browner. Microscopically, fatty deposits in the gland cells and Kupffer cells were nearly constant, and doubtless were associated with the hypercholesteremia that occurs during the feeding of rice (Umehara). Hemosiderin deposits occurred in one third of the cases; more rarely fibrosis (cirrhosis), with variable round cell infiltration. Yoshida (1924) likewise noted fatty infiltration and variable interlobular fibrosis and leukocytic infiltration in the liver in rabbits (more rarely in guinea-pigs) fed on boiled rice. In a case of infantile *beriberi*, Moore and Brodie (1927) observed cloudy swelling, vacuolation and deposit of pigment in the liver cells.

Pancreas: Ogata (1920) found an atrophy of the pancreas to half its original weight in rice-fed pigeons. The decrease was relatively less in chickens. The acini appeared atrophic, except near the pancreatic islets, where they were filled with zymogen granules (this observation confirming Segawa's). The islets became greatly increased in size and in number (fivefold per millimeter in chickens; fourteenfold in pigeons), developing out of the centro-acinar cells. Similar results were obtained by Ogata, Kawakita, Oka and Kagoshima (1921). Lopez-Lomba and Randoin (1923) reported a decrease of 24 per cent in the weight of the pancreas in *beriberi* in pigeons. Artom (1923) claimed that the pancreas in rice-fed pigeons differs from that in starved pigeons in that there is an increase in zymogen granules and a distention of some of the tubules through a retention of secretion. In rice-fed rabbits,

Murata (1923) found a marked loss in weight of the pancreas, with atrophy of the acini, but neither hypertrophy nor hyperplasia of the islets of Langerhans. Hoshi und Ukai (1926) likewise failed to see evidence of such changes in the pancreatic islets in fowls on a diet of polished rice. Riquier (1925) and Bierry and Kollmann (1927), on the other hand, confirming the observations of Ogata, found an increase in the number and the volume of the pancreatic islets in polyneuritic pigeons.

Kidney: Ogata (1920) demonstrated a marked increase in the weight of the kidney in rice-fed birds, the hypertrophy averaging 34 per cent in pigeons and from 20 to 43 per cent in chickens. The increased weight was associated with a (toxic?) nephritis. Leukocytic infiltration and tubular degeneration appeared in the affected renal areas, although the glomeruli were normal. Lopez-Lomba and Randoin (1923) found a smaller increase (about 10 per cent) in the weight of the kidney in pigeons on a special diet deficient in vitamin B. Murata (1923), on the other hand, noted an apparent average loss of about 9 per cent in the weight of the kidney in twenty rabbits with beriberi. The epithelium of the convoluted tubules appeared atrophic, without degeneration or necrosis. The glomeruli were normal. Cellular infiltration or changes were not observed in the interstitial tissue. Hyaline cylinders and cystic dilatations often occurred in the tubules, especially in the loops of Henle. These changes, together with albuminuria, characterize a nephrosis which occurs likewise in rice-fed rabbits without beriberi. Somewhat similar, but often more intensive, degenerative changes were observed by Kozawa and Yamamoto (1924) in the renal convoluted tubules of rice-fed rabbits.

Riquier (1925) found renal parenchymal changes in rice-fed pigeons, especially in the terminal stages. The changes included cloudy swelling, congestion and, rarely, small hemorrhages, but never the severer lesions described by some authors. Wake and Suzuki (1925), on the other hand, found a nephrosic, contracted kidney in seven of over 100 white rats on Hofmeister's diet deficient in vitamin B (polished rice and canned meat). Marked atrophic and degenerative changes, hyaline cylinders and allied signs appeared in the tubular epithelium, with slighter changes in the glomeruli. The interstitial connective tissue showed increase with round cell infiltration.

In Kepler's (1925) case of beriberi in an adult, the urine showed a slight amount of albumin with many casts, leukocytes and red cells, indicating renal involvement. Both cortical and medullary hemorrhages were noted in the kidney at necropsy by Moore and Brodie (1927) in their case of infantile beriberi. In beriberi in adults, Bernard, Bablet and Guillermin (1927) observed the renal condition as a toxic parenchymatous nephritis, not truly inflammatory in character. The changes

involved a progressive epithelial degeneration and necrosis, with congestion, and sometimes edema, intertubular hemorrhages or interstitial sclerosis. The kidneys at necropsy grossly appeared normal. Somewhat similar renal lesions were produced in the pig by infection with *Bacillus asthenogenes*. Renal disturbances in beriberi in man were noted also by Scott and Herrmann (1928).

**Reproductive Tract:** Dietary deficiency of vitamin B results in marked atrophy of the gonads (testis or ovary). This observation was made by Ogata and his associates, Lopez-Lomba and Randoin, Riquier and Simnitzky in pigeons and fowls, and by Murata in rabbits. The loss in the testes of pigeons may reach 90 per cent within from fifteen to twenty days (Simnitzky). This loss involves a progressive atrophy and degeneration of the seminiferous epithelium, which may finally be reduced to a single layer of supporting Sertoli cells (Murata). Murata (1923) found the interstitial tissue somewhat increased in rabbits, but Riquier (1925) was uncertain as to this change in pigeons. Ogata with others (1921) described an increase in the fatty granular content of the interstitial cells, which Simnitzky (1926) ascribed to an increased resorption of substances derived from the degenerated seminiferous epithelium.

The ovarian changes have been less extensively studied. In beriberi in rabbits, according to Murata, the atrophy involves the stroma, as well as the follicles, which are few and small. The interstitial cells are not apparent. Dulzetto (1927, 1927a) stated that the nuclei of the ovarian interstitial cells disappear, while the lipoidal granules become chemically changed so as to stain with hematoxylin instead of sudan III. However, germinal atrophy of the ovaries and the testes is not specific for the deficiency of vitamin B; it may appear in various forms of malnutrition, as observed by Yamasaki (1923) and many others.

Parkes and Drummond (1925) found in rats a decrease in fertility that was associated with degeneration of the testis and was, in general, proportional to the degree of the deficiency of vitamin B. In extreme cases, the testis sometimes failed to regenerate, so that sterility persisted in spite of recuperation of the normal body weight and vigor on restoration of the missing vitamin to the diet. Marrian and Parkes (1928) found that the degeneration of the testis in pigeons deficient in vitamin B is not necessarily a starvation effect, but is probably caused by lack of the antineuritic factor. Mattill (1927) and Evans (1928a) concluded that in the rat the degeneration of the testis hitherto ascribed to a deficiency of vitamin B is in reality due to an associated deficiency of vitamin E, and can usually be prevented by provision of the latter in the diet.

**Suprarenal Gland:** McCarrison's discovery of suprarenal hypertrophy in polyneuritic pigeons has received abundant confirmation, but

there is much confusion as to the details and significance of the associated changes. Bierry and his co-workers (1920) advanced the hypothesis (not confirmed by more recent work) that there is an associated hyperadrenalinemia which produces a generalized vascular sclerosis throughout the various organs. Hypertrophy of the suprarenal glands was noted in polyneuritic pigeons by Lopez-Lomba and Randoin (1923) and McCarrison and Norris (1924). Ogata and his associates (1920, 1921, 1924a) found in pigeons a suprarenal hypertrophy of only 17 per cent during the period of incubation (about the same as in starvation), and an increase to 79 per cent during the period of acute symptoms. In chickens the hypertrophy was smaller (from 25 to 56 per cent). Histologically, the suprarenal cortex showed marked hypertrophy with numerous mitoses, but not degenerative changes. The cholesterol esters decreased; other fats were unchanged. There was little, if any, change in the medulla; or in the chromaffin reaction. Beriberi in man differs, they claimed (1924), in that the hypertrophy occurs in the suprarenal medulla. According to von Beznak (1923), the two-fold or threefold enlargement of the suprarenal glands in beriberi is not due to simple inanition, since it does not occur in pigeons fed yeast only. The epinephrine content is decreased rather than increased. Riquier (1925) described the cortical changes in great detail. In advanced stages, there occurred marked vascular congestion, hypertrophy and hyperplasia of the cell-cords and reduction of fats. The medulla did not show any change except at death; then the cells appeared vacuolated and the nuclei pyknotic, while the chromaffin reaction was decreased or absent. Lasowsky and Simnitzky (1926), in pigeons, found the hypertrophy of the suprarenal glands proportional to the length of the period of deficient feeding. The hypertrophy was greater in the cortex than in the medulla. There was a progressive infiltration of fat in the cortical cells, due to hyperlipemia, with an associated hypertrophy and hyperplasia of the cells. The cells of the medulla also became hypertrophied, with nuclear enlargement and a decrease in chromaffin granulation. Kon and Drummond (1927) concluded that there is probably a hypertrophy of the suprarenal glands, but not any change in the content of epinephrine.

In beriberi in rabbits, according to Murata (1923), the increase of 35 per cent in the weight of the suprarenal glands is caused by cortical enlargement. There is hypertrophy, and probably hyperplasia, of the cells of the zona fasciculata. These cells usually show a marked increase in lipid content, an increase probably due to hypercholesteremia. Verzár and Péter (1924) found the weight of the suprarenal glands increased 70 per cent in rats and 100 per cent in rabbits. The increase was apparently due to cortical hypertrophy. Wax model reconstructions indicated an increase of about 50 per cent in the ratio of the cortex

to the medulla. They suggested that this cortical enlargement may have been a compensatory hypertrophy, in connection with a disturbance of the cholesterol metabolism. Drummond and Marian (1926) noted that in rats either starved or on a diet deficient in vitamin B the suprarenal hypertrophy was associated with hyperglycemia. Woollard (1927), however, did not discover histologic changes in the cortex or the medulla in Drummond's test rats. Kolliner (1927) noted variable changes in the ratio of the nucleus to the plasma of the suprarenal cells in rats on diets variously deficient. According to Marrian (1928) the suprarenal hypertrophy in pigeons deficient in vitamin B is caused chiefly by lack of the antineuritic ( $B_1$ ) factor, although  $B_2$  is contributory.

**Thyroid Gland, Parathyroid Glands and Hypophysis:** In polyneuritic pigeons, Ogata and his associates (1920, 1921) noted, in general, a decrease in the weight of the thyroid gland, but did not observe hyperemia, or any abnormal structure. Lopez-Lomba and Randoin (1923) reported a decrease of 28 per cent in the weight of the thyroid gland in polyneuritic pigeons. Riquier (1925) found in the thyroid gland a constant hyperemia with occasional hemorrhages, especially in pigeons that had died of beriberi. Desquamation of the follicular epithelium sometimes occurred, but marked changes in the colloid or the interstitial connective tissue did not appear.

In beriberi in rabbits, Murata (1923) observed a marked decrease in the weight of the thyroid gland, with, apparently, a follicular atrophy. Nicholson (1924) described a fragmentation and reduction in the number of mitochondria in the thyroid cells of rabbits and guinea-pigs under various conditions, including a deficiency of vitamin B. McCarrison (1927) reported an increase of from 50 to 100 per cent in the weight of the thyroid gland in rats on a defective diet, in which a deficiency of vitamin B was probably the chief factor. The goiter presented signs of hyperactivity, with later an exhaustion of the epithelium, which was replaced by nonsecretory cells and fibrous tissue. Somewhat similar results were obtained by Satwornitzkaja and Simnitzky (1927) in rats and pigeons.

Fukushi (1924) studied the thyroid gland in twenty-eight cases of beriberi in adults and in six cases in infants. The weight of the thyroid gland was usually above normal, although the size appeared subnormal in the adults. The follicles were decreased in size. In the adults, the epithelium was cubical or flattened (atrophic), desquamation frequent, necrosis rare, epithelial lipoids and pigment abundant, hemorrhages somewhat frequent and colloid thin. In the children, the epithelium was cubical, proliferation frequent, lipid scarce, pigment absent, colloid thin and interstitial connective tissue somewhat increased.

In polyneuritic pigeons, Ogata (1920) noted a decrease in the size of the parathyroid glands, with some cellular changes. Riquier (1925),

however, found the parathyroid glands normal. Tanabe and Yoshimura (1920) gave measurements on the size of the parathyroid gland in thirty cases in man, but his conclusions were uncertain in the absence of norms for comparison. The parathyroid glands presented a parenchymatous hypertrophy, with little adipose tissue. The light chief cells appeared to be increased in relative frequency.

Ogata (1920) did not observe in rice-fed fowls and pigeons any definite change in the weight or structure of the hypophysis; but with his associates he later (1921) found an increase in weight with colloid occurring in the cell-cords of the hypophysis. This was confirmed by Riquier (1925), who observed also congestion with frequent mitoses and an increased lipid content in the chromophil cells. Murata (1923) found in beriberi in rabbits an apparent slight loss of the weight of the hypophysis. Satwornitzkaja and Simnitzky (1928) noted increased vacuolation, especially of the basophil cells, which was more pronounced in pigeons than in rats.

**Thymus and Spleen:** Marked atrophy of the thymus in rice-fed pigeons was observed by Ogata and his associates (1920, 1921), Lopez-Lomba and Randoin (1923) and Riquier (1925). In beriberi in rabbits, Murata (1923) likewise noted this extreme thymic atrophy, even with relatively slight loss in body weight. The thymic lymphocytes underwent retrogression and Hassall's corpuscles became rare.

Marked atrophy of the spleen in rice-fed pigeons was found by Ogata (1920), Lopez-Lomba and Randoin (1923) and Riquier (1925); and in beriberi in rabbits by Murata (1923). This atrophy (like that of the thymus) apparently occurred irrespective of loss in the weight of the body. Atrophy was observed in the red pulp as well as in the white pulp, and hemosiderin deposits were increased in the reticulo-endothelial cells. Riquier also noted a decrease in size with follicular atrophy of the lymphatic glands in various regions (pigeons). The bone marrow showed enlargement of the adipose cells, but a decrease in the hemoblastic elements (myelocytes, erythroblasts and megakaryocytes).

**Blood:** In general, the atrophy of the hematopoietic tissues tends to cause anemia during inanition from a deficiency of vitamin B, but the results appear variable. Ogata (1920) observed in chicks on a diet of rice (with forced feeding) a preliminary increase in the erythrocyte count, with a decrease later. The leukocyte count (polymorphonuclears) tended to increase, although the lymphocyte count remained unchanged. Ogata and his associates (1924) held that a decreased number of both erythrocytes and lymphocytes is one feature distinguishing B-avitaminosis of animals from beriberi in man. Riquier (1925) in polyneuritic pigeons found a progressive decrease in the erythrocyte count (from 4,500,000 to 2,500,000). The leukocyte count (pseudo-eosinophils) and



the number of platelets increased, and then decreased in the final period. Morphologic changes in the red cells (poikilocytosis and like conditions) were also noted by Riquier and Ogata. Barlow and Biskind (1928) found a decrease in red cell count, associated with relative hydremia, Suzuki (1924) also reported anemia and lymphopenia in test pigeons. De Gasperi (1926), on the other hand, did not find any significant change in the erythrocyte count; but found an increase in the percentage of polymorphonuclear neutrophils and in that of basophils, with a corresponding relative decrease in the percentage of lymphocytes. Little change in the fat and lipoid content of the blood was found by Tawamura (1924) in beriberi in chickens, and by Iwatsuru (1925) in rabbits. In beriberi in rabbits, anemia was observed by Murata (1923) and Verzá and Kokas (1924), which accords with the marked atrophy of the hematopoietic tissue noted by Ozawa (1922) and Murata (1923). The adipose bone marrow underwent a gelatinous metamorphosis, as in starvation. Sherif and Baum (1927) concluded that a deficiency of vitamin B did not have any definite effect on the thrombocyte or erythrocyte count in rats.

**Skeleton:** In addition to the aforementioned atrophy of the bone marrow, osteoporosis, with a tendency to spontaneous fractures, was found in beriberi in rabbits by Ozawa (1922) and Murata (1923). Also, hemorrhages in the bone marrow were noted occasionally by Ozawa (1922) in rabbits and by Sure (1927, 1927a) in young rats. Sure and Schilling (1928) found these hemorrhages conspicuous and nearly constant.

*Effects of Deficiency of Vitamin C (Antiscorbutic).*—Epidemic scurvy has been one of the scourges during both remote and recent years of war and famine, especially in Russia. Tschernorutzki (1922) reported observations on 4,227 cases in adults. According to Schagan (1924), the highest incidence was in children. In the St. Petersburg Children's Clinic, cases of scurvy were rare before the war, but formed 11.3 per cent of all cases in 1920. Beeuwkes (1926) reported that in certain Russian districts in 1921 over 75 per cent of the population had scurvy, with a mortality reaching 50 per cent of the hospitalized cases. "Hunger edema" (in which, as has been mentioned, a deficiency of protein is probably the chief factor) was a frequent complication, according to the literature reviewed by Herzenberg (1926). Shipley and Chavarria (1924) noted a great increase in infantile scurvy after the pasteurization law became effective in Baltimore, in 1917.

Kompanejetz (1923) observed that rhinitis sicca anterior was often present in scorbutic Russian soldiers. The septal wall appeared scabby and there was an associated epistaxis in about one third of all the cases. The literature cited by Place (1925) indicates that exophthalmos, pro-

duced by orbital hemorrhages, appears in about 10 per cent of all cases of infantile scurvy. Bullowa (1927) described a case of mixed scurvy and beriberi in a hotel porter who had lived for four and a half months on tea and bread. Abels (1924) maintained that "dysergy," or predisposition to infection, is a characteristic feature in scurvy, and that many of the usual symptoms (including the hemorrhages) are chiefly secondary to the associated infections.

The variation in susceptibility to scurvy according to the species is well known. Béard (1926) found that for normal growth in the mouse (as in the rat), vitamin C is apparently not a dietary essential. Thurston, Eckles and Palmer (1926) reached a similar conclusion for the calf. Goss (1925) and Meyer and McCormick (1928, 1928a) gave detailed accounts of the lesions in scorbutic guinea-pigs. Anderson and Smith (1924) concluded that the loss in weight in guinea-pigs during scurvy cannot be attributed to simple inanition alone.

L. F. Meyer (1923) recognized three stages in human scurvy: (1) a latent stage (which may continue indefinitely), characterized by a tendency to hemorrhages, owing to abnormal permeability of the vascular walls, especially in the skin and mucosae; (2) appearance of gingival hemorrhages and pains in the long bones and costochondral joints, and (3) development of the typical scorbutic symptoms, with involvement of the supporting tissues, widespread hemorrhages and other conditions. Andresen (1923) described (1) a latent scorbutic stage, with pains along the nerve trunks and cutaneous cyanosis; (2) a stage of active scurvy, with typical hemorrhages and other characteristic conditions, and (3) a stage of retrogression, with resorption of the hemorrhagic exudates, scleroderma, etc. Tschernorutzki (1922) gave detailed statistics on the occurrence of the various symptoms in scurvy in adult human beings. Friderichsen (1927) emphasized the variation in localization of early scorbutic symptoms in children according to age. In infants, the dominating symptoms appear, he stated, in the long bones. In older children, the muscular system is affected more, "growing pains" being a frequent prescorbutic myopathy. In older persons, extensive hemorrhages in the skin occur. Shattuck (1928) concluded that well marked scurvy in the adult may easily pass unrecognized.

Mouriquand and his associates (1924) found that although adult guinea-pigs might recover fully on an antiscorbutic diet, about 65 per cent of the younger animals failed to recuperate and passed into a chronic condition resembling athrepsia in man. Even those apparently fully recovered appeared more susceptible to a second attack of scurvy. This was at first ascribed to persistent lesions in the bone marrow, but later (1924a) to lesions in the liver. Fujihira (1923), however, did not find an increased susceptibility to a second attack of scurvy in guinea-pigs.

Smith (1927) found that guinea-pigs on a basal scorbutic ration died in from ten to thirty days with acute scurvy. Those receiving, in addition, an insufficient dose of orange juice (0.5 cc. daily) usually lived from six to eight months in a debilitated state somewhat resembling infantile scurvy, with loss of weight, paralysis of the limbs, and other typical conditions. Gerstenberger and his associates (1924) noted that the symptoms of scurvy appeared to be less severe in pregnant guinea-pigs. Fetal scurvy in guinea-pigs was observed by Meyer and McCormick (1928, 1928a).

Wolbach and Howe (1925, 1925b, 1926) concluded from experiments on guinea-pigs that the scorbutic state affects primarily the supporting tissues, in which the cells are unable to produce and maintain the normal intercellular substances and structures. The hemorrhagic tendency is increased by the lack of intercellular cement in the endothelium, as held by Aschoff and Koch. Proliferative capacity is not lost by the endothelium, fibroblasts or osteoblasts. Meyer (1926) and Meyer and McCormick (1928, 1928a) found in scorbutic guinea-pigs a visceral fatty degeneration. This appeared to be secondary to a generalized autolysis, resulting in an extensive destruction of both the voluntary and the involuntary musculature, nervous system, skeleton, lungs and abdominal viscera. Meyer held that this widespread cellular degeneration, rather than defects in the cement substance or supporting tissues, is the fundamental lesion in scurvy. Stettner (1925) contributed a critical review of the literature on the etiology and pathology of scurvy and rickets.

Brouwer (1927) noted granular hematogenous pigment in various organs (spleen, suprarenal, alimentary canal, liver) of scorbutic guinea-pigs. Of the weights of the various organs, that of the eyeball and that of the kidneys remained nearly stationary; that of the suprarenal glands increased; that of the thymus (and to some extent the weights also of the heart, the pancreas, the thyroid and, probably, the ovary and the liver) decreased; while that of the spleen was highly variable.

Blood Vessels and Blood: Meyer (1926) and Meyer and McCormick (1928, 1928a) observed that the blood vascular endothelium in scorbutic guinea-pigs becomes swollen and detached, and that the vascular walls are deficient. The conclusions of Wolbach and Howe concerning endothelial cement have been mentioned. Bencini (1926) noted an abnormal extravasation of fluid on the intravenous injection of physiologic sodium chloride solution into the vessels of scorbutic guinea-pigs, resulting in perivascular edema around the great vessels in the abdomen, the neck and the hind limbs. Stefko (1927a) described in detail the degenerative changes in the walls of the intestinal blood vessels in scorbutic (?) victims of famine, with hemorrhagic diathesis. Novodvorskiy (1928) also described the blood vascular changes in scurvy in man.

Anemia, according to Aron (1922), is an early symptom in infantile scurvy. Schagan (1924) found the blood picture variable, with the erythrocyte count ranging from 3,000,000 to 4,500,000; the leukocyte count from 4,000 to 6,000 (of which the polymorphonuclear neutrophils made up 60.5 per cent, the lymphocytes 34.5 per cent, the eosinophils 1.5 per cent, the basophils 1 per cent and the monocytes 2.5 per cent). The leukopenia usually disappeared during convalescence. Ossinowski (1924) noted hypolymphocytosis (lymphopenia) in scorbutic Russian children. Shipley and Chavarria observed the erythrocyte count dropping as low as 2,480,000; and the leukocyte count varying from 5,000 to 15,000, even in apparently uncomplicated cases. The differential counts are also given. The effects of infectious complications are described. A relative lymphocytosis with a decreased number of neutrophils was observed by Tschernorutzki (1922) and Andresen (1923) in scorbutic Russian adults. Oppel and his co-workers noted anemia with thrombopenia and leukopenia in their study of scurvy in rabbits and in man. In infantile scurvy, Carbonara (1928) observed moderate anemia, poikilocytosis and anisocytosis, with marked decrease in hemoglobin content. In experimental scurvy, the changes in the blood were slight.

In scurvy in rabbits, Findlay (1923) and Bencini (1926) noted leukopenia. In guinea-pigs, Lesné and his associates (1923) found the red and the white cell count variable according to the stage of scurvy. Liotta (1923) noted a progressive anemia with slight leukocytosis, the differential count showing mononucleosis, neutropenia and eosinophilia. Verzáar and Kokas (1924) did not find any change in either the white or the red cell count. Sherif and Baum (1927) likewise failed to observe any change in red cells or thrombocytes. Trentini (1927) noted an increase in the number and the size of the fat droplets in the monocytes of scorbutic guinea-pigs. Meyer and McCormick (1928, 1928a) found a decreased number of erythrocytes and a decreased number of lymphocytes, but an increased count of polymorphonuclears.

Gottschalk (1923) ascribed the anemia of infantile scurvy to a primary lesion of the bone marrow. In the bone marrow of scorbutic guinea-pigs, Findlay (1923) observed a gelatinous degeneration, and Mouriquand, Michel and Bernheim (1924) noted fibrosis with a greatly decreased number of lymphoid cells.

**Skeleton:** In addition to the aforementioned changes in the bone marrow, the effects of scurvy on the skeleton in guinea-pigs will now be considered. Shinya (1922) found that transplantation of metatarsal bones or phalanges from scorbutic into healthy guinea-pigs succeeded in one third of the cases, but the converse experiment failed. In guinea-pigs on scorbutic diet, according to Watanabe (1924) and Schilowzew (1928), fractured bones are not repaired, and the resorption

of traumatic exudates of blood is greatly retarded. On the other hand, underfeeding alone does not prevent new formation of bone. Murata (1924) concluded that the essential skeletal lesion in experimental scurvy is a degeneration of the periosteum and endosteum, causing an inability to ossify. Merely connective tissue cells are formed, which, as a granulation tissue, tend rather to resorption of bone.

Wolbach and Howe (1925b, 1926) found that during scurvy the formation of bone ceases immediately, although in places osteoblasts (and fibroblasts in general) continue to proliferate. These can form an ossified matrix within forty-eight hours, if antiscorbutic substances are fed. During scurvy, incisions in the bone are not repaired. Israel and Fraenkel (1926) observed marked retardation of the formation of the callus and of the healing process in fractures of the femur in scorbutic guinea-pigs.

Höjer and Westin (1924, 1925) and Westin (1925, 1925a) described the changes in the jaw bones as well as the teeth of scorbutic guinea-pigs. Meyer and McCormick (1928) observed proliferative changes in the costal cartilages and the bone marrow, with marked degeneration and disintegration of the walls of the blood vessels. According to Ossinowski (1924), in scurvy in man the skeleton is involved more frequently and more severely in children than in adults.

Noteworthy advances have recently been made in the roentgenology of the scorbutic skeleton. The excellent work of Wimberger (1923, 1924, 1925), when compared with that of Tobler (1918) from the same institution (Pirquet's pediatric clinic in Vienna), reveals striking progress both in the technic of making the plates and in the skill of interpretation. Wimberger emphasized the diagnostic importance of Fraenkel's "white line" (the "Trümmerfeldschatten"), which was questioned by Tobler and some other workers. It is admitted, however, that a somewhat similar shadow may appear in the zone of new calcification in healing rickets, and puzzling pictures may occur also in cases of intermittent or healed scurvy, as well as in the (not infrequent) mixture of rickets and scurvy.

Two other interesting features in the roentgenography of scurvy were presented by Wimberger. The first is the clear zone of rarefaction, corresponding to the trabecular resorption in the "Gerüstmark" (fibrous marrow) area of the diaphysis, adjacent to the denser "Trümmerfeld" zone. This rarefaction occurs likewise in the epiphyses, which become light, except in a denser peripheral border or ring (corresponding to a "Trümmerfeld"). The light epiphyseal centers had been observed previously by Reyher (1911) and Gött (1918), who did not recognize their diagnostic importance. Gött claimed that they appear not only in scurvy, but in various other atrophic conditions of the skeleton. Wimberger held that they are characteristic of scurvy,

and may persist in the epiphyses even years after clinical recovery. The occurrence and diagnostic importance of Wimberger's ring was confirmed by Pelkan (1925), Schwartz (1927) and Bromer (1928). Nassa (1925) held that the ring occurs only in cases of combined scurvy and rickets.

The second feature of interest is the appearance of from two to four, or more, cross-lines (near the end of the diaphysis), which represent former "Trümmerfeld" zones persisting from healed intermittent scurvy. These lines were previously noted by Tobler (1918) and especially by Frank (1920). Stettner (1925) and Harris (1926, 1928) think they represent cessations of osseous growth, which may occur normally during adolescence as well as following rickets or any form of acute illness or starvation. Bromer (1928) gave a thorough review of the literature together with data from fifty-six original cases illustrating the points in the roentgenologic diagnosis of scurvy.

**Teeth:** Williams (1923) reported profound degenerative changes in both the enamel and the dentine of guinea-pigs subjected to vitamin deficiencies resulting in a condition related to scurvy. Wolbach and Howe (1925, 1925b, 1926) paid special attention to the teeth, in which the earliest effect of scurvy is found. The odontoblasts in the incisor teeth become separated from the dentine and undergo striking changes in size, arrangement and staining reaction. Normal structure may be reestablished within forty-eight hours after the feeding of antiscorbutic foods. Smith (1927) noted frequent fractures of the teeth in chronic scurvy of guinea-pigs; while Meyer and McCormick (1928, 1928a) found hemorrhages in the pulp of the incisors.

An especially thorough study of the changes in the teeth of scorbutic guinea-pigs was made by Höjer and Westin (1924, 1925) and Westin (1925, 1925a, 1926). The principal lesions found were: (1) the gradual change and disappearance of the odontoblastic layer; (2) the amorphous calcification of the predentin and the absence of Tomes' canals in this layer; (3) the old dentin's becoming porous; (4) the new formation of pulp bone instead of dentin; (5) hyperemia and sometimes hemorrhages, necroses and subsequent hydropic changes in the pulp and (6) later variable atrophy and resorption of the pulp bone, dentin and pulp tissue.

**Alimentary Tract:** Oral lesions, especially of the gums, are characteristic symptoms of scurvy in man. The gingival changes were described by Tschernorutzki (1922), Ossinowski (1924) and Scholle (1924). They occurred in 90 per cent of the Russian adults and in 100 per cent of the children. The stomatitis became gangrenous in 13 per cent of the cases, according to Schagan (1924), and in 15 per cent of Tschernorutzki's 4,227 cases. Mouriquand and his co-workers (1924)

did not find any significant lesions in the intestines of scorbutic guinea-pigs, although intestinal atrophy was noted in those which failed to recover when refed a normal diet. Carra (1925) described areas of variable degeneration in the mucosa and muscularis mucosae of the small intestine, and to a lesser extent in the stomach and large intestine, in scorbutic guinea-pigs; while Guarino (1927) found gastric congestion, hemorrhages and disappearance of the secretory granules in the gastric gland cells. Mucohemorrhagic diarrhea was described by Ossinowski (1924) as a grave symptom in infantile scurvy. According to Scholle (1924), the intestinal hemorrhages are produced by ulceration of the intestinal wall.

**Liver:** In the liver of scorbutic guinea-pigs, Murata (1922) found in 80 per cent of the cases grayish spots of variable size. On microscopic examination, these spots presented necrotic areas, which were interpreted as anemic infarcts due to thrombosis of branches of the portal vein. Lopez-Lomba and Randoin (1923a) observed an increase in the weight of the liver. Carra (1925) noted a fatty infiltration but not any degenerative changes in the hepatic glandular epithelium. Mouriquand and his associates (1924, 1925) found marked lesions in the liver of previously scorbutic guinea-pigs that had failed to recover fully and had passed into a chronic state of cachexia after being placed on a normal diet. In these cases, the liver appeared atrophic, with enormous capillary dilatation and multiple hemorrhages. The liver cells were atrophied, without fatty degeneration, and the nuclei were of normal size. Meyer and McCormick (1928, 1928a) noted fatty degeneration of the liver as one of the most conspicuous lesions in scorbutic guinea-pigs. Detached masses of liver cells were seen in the large hepatic veins.

**Pancreas:** Murata (1922) and Carra (1925) observed a slight hypertrophy and hyperplasia of the pancreatic islets of Langerhans in scorbutic guinea-pigs. Murata pointed out the probable significance of these changes in relation to the co-existent hyperglycemia. Fatty degeneration in the pancreas was noted by Meyer and McCormick (1928, 1928a). According to Löwy (1923), the pancreatic islets appeared strikingly larger and more numerous in scorbutic guinea-pigs; but changes were not found in starvation.

**Spleen and Thymus:** In scorbutic guinea-pigs, Lopez-Lomba and Randoin (1923a) found little, if any, change in the weight of the spleen, but Mouriquand and his associates (1924) observed splenic atrophy. Brouwer (1927) found the spleen variable in weight, with deposits of hematogenous pigment. Oppel and his fellow research workers (1924) suggested that the hemolytic action of the spleen is inhibited by a suprarenal hormone, which is decreased in scurvy.

A marked atrophy of the thymus was noted in scorbutic guinea-pigs by Morikawa (1920), Lopez-Lomba and Randoin (1923a) and Brouwer (1927).

Kidney: In scorbutic guinea-pigs, Murata (1922) observed occasionally what he termed "metastatic calcification" in the kidney, although Lopez-Lomba and Randoin (1923a) found little, if any, change in the weight of the kidney. Meyer (1926) and Meyer and McCormick (1928, 1928a) noted a marked fatty degeneration in the epithelium of the kidney and other organs. Mouriquand and his associates (1924) did not find any significant lesions in the kidneys of athreptic guinea-pigs that failed to recover after antiscorbutic feeding.

Reproductive System: A marked atrophy of the testis in scorbutic guinea-pigs was noted by Morikawa (1920); while Lopez-Lomba and Randoin (1923a) found only a slight loss of 12 per cent. Mouriquand, Michel and Sanyas (1923) observed an early effect on spermatogenesis, with almost complete destruction of the seminiferous epithelium in some places. Abnormal spermatic cells and spermatozoa were also observed. Medes (1926) and Lindsay and Medes (1924, 1926) found but little apparent change in the weight of the testis after ten days on a scorbutic diet. The blood vessels appeared congested, with degeneration of the seminiferous epithelium in some tubules. Multinucleated or giant cells, such as occur during starvation, were not found. Other tubules showed normal spermatogenesis. Guinea-pigs, previously scorbutic for from thirty to forty days, had almost completely recovered the normal structure of the germinal epithelium after seventeen days on an antiscorbutic diet. Disintegration of the seminiferous epithelium was noted by Meyer and McCormick (1928, 1928a).

Marked atrophy of the ovary in scorbutic guinea-pigs was also observed by Morikawa (1920), but observations of the structure were not recorded.

Endocrine Organs: A marked increase in the weight of the thyroid gland in scorbutic guinea-pigs was noted by Lopez-Lomba and Randoin (1923a). Brouwer (1927), however, found a decrease. Mouriquand, Michel and Sanyas (1923) observed a slight congestion, a tendency to sclerosis and, often, small follicles. Morelli and Gronchi (1927), on the other hand, did not find sclerosis, but often found signs of hyperplasia and hypersecretion, especially in the thyroid glands of guinea-pigs dying early with atypical symptoms. Löwy (1923) did not see any histologic changes in the thyroid gland. The cells of the parathyroid glands appeared small. Harris and Smith (1928) found the follicular thyroid cells increased in number and height, with the colloid vacuolated and decreased in amount. Changes were not noted in starvation.

Suprarenal Glands: The marked hypertrophy of the suprarenal glands in the scorbutic guinea-pig was confirmed by Lopez-Lomba and



Randoin (1923a), and Brouwer (1927). Morikawa (1920) ascribed this hypertrophy to the co-existent condition of simple inanition. Mouriquand, Michel and Sanyas (1923) found the suprarenal glands congested (sometimes enormously), especially in the medulla, more rarely in the zona fasciculata. The superficial part of this zone presented a variable degree of fatty infiltration. Lindsay and Medes (1926a) noted changes similar to those previously described by McCarrison, with a variable amount of hemorrhagic infiltration in the cortex and medulla.

Morelli and Gronchi (1927) in the earlier stages of scurvy in guinea-pigs found signs of increased activity of the suprarenal glands, as shown by a siderophil substance, fuchsinophil granules, lipoids and doubly refractive fats. In later periods, there was an increase of fuchsinophil granules and siderophil cells, but a diminution of lipoids and doubly refractive substances. Most important was the cortical hyperplasia, with numerous mitoses; also amitoses. Besides these progressive changes, there were also regressive phenomena, due to numerous hemorrhagic foci, with zones of cloudy swelling and nuclear degeneration (pyknosis, chromatolysis and other typical conditions). In the medulla, the chromaffin reaction decreased, up to complete disappearance. On refeeding a complete diet after the first appearance of scorbutic symptoms, some of the animals recovered promptly; others died after from twenty to fifty days, with hemorrhagic lesions and fatty degeneration of the suprarenal glands. Meyer and McCormick (1928, 1928a) also mentioned degenerative changes in the suprarenal epithelium.

According to Rowles (1925), the apparent increase in the weight of the hypophysis in the scorbutic guinea-pig is due to congestion in the pars anterior, as shown by volumetric analysis. The parenchyma actually decreases in volume, with karyorrhexis and karyolysis in the later stages. Meyer and McCormick (1928a) also found various hemorrhagic and degenerative lesions in the nervous system and skeletal muscle.

*Effects of a Deficiency of Vitamin D (Antirachitic).*—The recent literature on the etiology and pathogenesis of rickets was reviewed by Howland (1923), Stettner (1925) and Hess (1928). McCollum's demonstration of the antirachitic vitamin D as distinct from vitamin A was accepted by Bloch (1923) and by most of the recent workers in this field. Davis (1923), however, and some more recent workers still supported the theory that vitamin A is the antirachitic factor. Thus, Zilva and his associates (1924) concluded that in pigs experimental rickets was produced when the amount of vitamin A present in the diet was sufficient to support growth but insufficient for ossification. According to Bohstedt and his associates

(1926) the "stiffness," or rickets, in swine is a disorder involving a deficiency of calcium, as well as of vitamins A and D. Marfan (1925) and Debray (1925) maintained that rickets in man is essentially a chondromyelitis (due chiefly to infections or toxins), and distinct from the experimental rickets in rats, which is essentially a chondroperiostitis.

Lobeck (1924) concluded that for production of rickets in rats, a deficiency of vitamin A is not essential (vitamin D was not recognized); that the proportions of calcium and phosphorus salts are of minor importance; and that absence of light is the effective agent. Lang (1925) held that both a dietary deficiency of vitamins and a lack of sunlight are the pathogenic factors. Various workers have recently demonstrated that vitamin D can be produced by ultraviolet radiation of a provitamin substance (ergosterol), either within the living body or in the food outside the body. This topic was reviewed by Hess (1928). Orgler (1927) concluded that rickets is essentially a disturbance of the intermediary calcium and phosphorus metabolism, which is normally regulated through (1) small amounts of vitamin D (arising from provitamin, activated by ultraviolet rays) and (2) endocrine secretions regulating salt metabolism. Von Bosányi (1925) emphasized the bone marrow as the seat of the antirachitic factor, since marrow extracts prevented or cured rickets. Holst (1927) still refused to accept the theory that rickets is caused by a deficiency of any vitamin; he believed that it is produced by some toxic substance present in cereal diets.

As to the frequency of rickets in man, Hess of New York held that it is the most common malnutritional disease, and that fully three fourths of the infants in the great cities are affected in some degree. Similarly, Blum and Mellion (1926) of New York reported that "fully 75 per cent of all artificially fed and perhaps 50 per cent of all breast fed infants manifest evidences of mild rickets at some time during the first two years of life." Beeuwkes (1926) found 80 per cent of the children with the disease in some districts of Russia. Schlesinger (1924) reported much smaller figures for German infants and small children, among whom the proportion of those that were rachitic reached a maximum of 25 per cent in 1918-1919, decreasing later to 15 per cent, but increasing again to 20 per cent in 1923.

Hess and Weinstock (1926) concluded that in the rat and in the human species rickets can be modified to some degree, but not entirely prevented, by the character of the maternal diet. Grant and Goettsch (1926), on the other hand, showed that young rats develop severe rickets when the mother's reserve of antirachitic vitamin is depleted by continuous reproduction in darkness and on diets deficient in this vitamin. Hess and his associates (1928) observed that vitamin D is essential for the embryonic development of both fish and chick.

The importance of age as a factor in predisposition to rickets was emphasized by Eckstein (1924) and Rabl (1925). Rabl found that in young rats (from 5 to 12 weeks old) a deficiency of light and of vitamin D usually caused rickets, while in older rats it produced merely osteoporosis. Abels (1927) stated that late rickets (adolescent osteopathy) occurs much more frequently in males than in females.

The variation in susceptibility according to the species appears in rickets as well as in other disorders due to dietary deficiencies. Beard (1926) could not produce rickets in mice. The rabbit also was generally found not susceptible to rickets, but Goldblatt and Moritz (1925) were successful with forced feeding of a diet deficient in phosphorus and the antirachitic factor but rich in calcium. Okamoto (1924) likewise produced rickets in young rabbits by a diet which causes scurvy in guinea-pigs. The effect of a deficiency of vitamin D in reducing the natural immunity against infections in various animals was shown by Mellanby (1926) and Eicholz and Kreitmaier (1928). Green and Mellanby (1928), however found that vitamin D does not prevent the pyogenic lesions due to deficiency in vitamin A.

**Weight and Length of the Body:** From observations on 870 rachitic infants, Wiltsche (1924) concluded that in the first half year, the growth in the length of the body is markedly retarded, even in mild cases. Both the trunk and the limbs are involved. The weight is correspondingly retarded, but the girth of the chest is above normal. In the second half year, the results are nearly the opposite, both stature and weight appearing above normal. Abdominal enlargement (present in 90 per cent of all cases) is due to gaseous distention of the intestines. Variot and Nazarie (1925, 1926) studied 233 rachitic children, of whom only fifteen were less than 6 months of age, the others being from 6 months to 2 years old. As to stature, the following percentages were found: 20.2 above normal; 44.3 normal and 35.5 below normal; as to weight: 31.3 above normal; 31.8 normal, and 36.9 below normal. Weight and stature ran parallel in 85 per cent of the cases, with dissociation in 15 per cent. Children surviving rickets are evidently, in most cases, able to recover later any deficiency in height or weight, according to the observations of Chase (1914) in Munich and of Wimberger (1925) in Vienna.

**Teeth:** Blum and Mellion (1926) reviewed the question concerning the diagnostic value of delayed dentition as a sign of rickets. They concluded that, although the dentition is usually delayed, even in mild rickets, this has little diagnostic significance since there is a normal variability in the time of the eruption of the deciduous teeth. Variot and Nazarie (1925, 1926) found that the eruption is retarded less frequently than is generally believed. Among thirty-seven atrophic rachitic infants, thirty-two had cut their teeth normally. Among

sixty-three hypertrophic rachitic infants, the dentition was normal in fifty-three. The relation of variously deficient diets to caries of the teeth was discussed by Mellanby, Pattison and Proud (1924). By feeding experiments on institutional children, it was shown that dental caries is less marked in those on diets short of cereals but rich in calcium and calcifying vitamin.

**Skeleton:** According to Moore (1924), the first skeletal signs of infantile rickets are craniotabes (most easily determined at the mastoid fontanel), deformities of the chest and costomalacia or softening of the sternal ends of the ribs. Both genu valgum and genu varum are always preceded by abnormal lateral motility of the knee joint, which is often the first sign of rickets in the leg. From a study of 870 infantile cases, Wilsche (1924) concluded that, simultaneously with the craniotabes, a slight "rosary" appears on the fourth, fifth and sixth ribs. The epiphyses of the limbs are involved somewhat later, the upper usually earlier than the lower (this observation confirmed Stoelzner's, and was opposed to Guérin's observations).

Abels and Karplus (1927) regarded the presence of craniotabes or an enlarged fontanel at birth as a prerachitic symptom. In some cases, as shown by Koeppe (1926) and Bohe (1928), there may be a rachitic distention of the ventricles of the brain without any external enlargement of the cranium. This condition, which can be diagnosed by the roentgen ray, is designated by Koeppe as hydrocephalus occultus.

Huldschinsky (1928) concluded that the craniotabetic thinning of the cranium does not correspond to the ordinary skeletal softening in rickets. He interpreted it rather as osteoporotic thinning of the cranial wall, secondary to the increased growth of the brain in rickets. Craniotabes responds to antirachitic therapy much less readily than do the ordinary skeletal lesions.

The interpretation of roentgenograms in connection with rickets (as also in connection with scurvy) has received much attention in recent years. The subject was discussed at length by Weech and Smith (1923), Lesné, Mahar and Colaneri (1924), Wilson (1926) and Wimberger (1923, 1925), whose contributions are especially noteworthy. Groover, Christie and Merritt (1925) also made an extensive and valuable study of 926 cases. A clinical diagnosis of rickets was made in 68.7 per cent of the cases, an x-ray diagnosis in 66.5 per cent. In the incipient cases, the x-ray diagnosis is apparently far more accurate than the clinical diagnosis. Hamburger and Siegl (1928) noted the deceptive appearance of a "pneumothorax rachiticus," caused by the thoracic deformity.

From the work of Haffa (1924) and of Breus and Kolisko, it is apparent that the deformities of the adult pelvic skeleton (which are of especial importance in relation to child-birth) often appear during

rickets in childhood. The pelvic deformity is usually, but not always, proportional to the severity of the rickets in general. Reyher (1922) and Koehler (1924) concluded that the calcification of the bony epiphyseal nuclei of rachitic children is in general not appreciably delayed. Plaut (1924, 1924a) held that during mild infantile rickets the centers of ossification appear without delay, as shown by the x-rays. In moderate or severe cases, the centers of ossification fail to become visible by x-rays; but in reality the centers are laid down in uncalcified form at the normal time, as shown by the extreme rapidity with which large centers later become visible through calcification when the healing process begins (as was noted by Fraenkel and Lorey). Only in the severest cases of rickets is there a true retardation in the centers of ossification. Lewin (1927) found the appearance of an epiphysis within an epiphysis at the lower end of the femur and the upper end of the tibia in a child who had apparently suffered from intermittent rickets. As mentioned before, in the discussion of scurvy, difficulty is sometimes encountered in differential diagnosis between scurvy and rickets by the roentgenologic method, especially in cases of intermittent or coincident scurvy and rickets.

Lobeck (1924) described in detail the histologic changes in the skeleton in rats with experimental rickets, which he considered equivalent to rickets in man. Marfan (1925) and Debray (1925), however, contended that while the lesions of the bones are somewhat similar, the osteoid tissue is formed in the rat chiefly from the periosteum (perichondrium), while in rickets in man it is formed largely from marrow elements. Thus (as has been mentioned), rickets in rats is considered by them as essentially a chondroperiostitis; rickets in man as a chondromyelitis. Dalyell and Mackay (1923) demonstrated that histologic evidence of rickets may appear in infants without any clinical or roentgenographic symptoms of the disease. Brockman (1927) described certain skeletal peculiarities found in "renal rickets," associated with chronic interstitial nephritis in children. These peculiarities are ascribed to the toxic condition resulting from renal insufficiency.

Neubauer (1925) demonstrated that in rachitic rats the skull becomes relatively shorter, that is, brachycephalic. From a study of the limb bones of rachitic pigs and calves, McGowan (1924) concluded that the structure in the affected epiphyseal regions is modified to a considerable extent by the abnormal mobility of these parts. Bohstedt and his associates (1926) found that the stiffness, or posterior paralysis, in rachitic pigs is caused by fractured vertebrae, which project into the vertebral canal and compress the spinal cord. "Beading" of the ribs is usually present, although the histologic structure often differs from that in typical rickets or osteoporosis. Nonidez (1926) described the skeletal lesions in avian rickets.

**Bone Marrow:** The importance of the lesions of the bone marrow in rickets in man was emphasized by Marfan (1925) and Debray (1925), as has been mentioned. According to Debray, the medullary lesions were discovered by Cornil and Ranvier, and have since been studied in detail by Marfan and others. The changes, which DeBray held occur in rickets in man, but not in experimental rickets in animals, include a proliferation of marrow cells, normoblasts and eosinophils; a degeneration of neutrophil myelocytes; the presence of megakaryocytes, myeloplaxes and small mononuclears, and the appearance of marrow cells around vessels and even under the periosteum. The capillaries appear congested, sometimes with small hemorrhages. In late stages, there is a proliferation of the fixed elements with variable fibrosis. These lesions in the marrow are correlated with changes in the blood, as shown by DeVilla and Cartia (1925) through smears of marrow from the tibia (Caronia's method). The marrow cell counts in twenty-two rachitic children indicated in general an increased myelopoiesis and erythropoiesis, with a larger percentage of myeloblasts, hemocytoblasts and immature red cells. The observations on the blood recorded by Maurer and his associates (to be mentioned later) also indicate the involvement of the bone marrow in rachitic rats.

**Blood:** The results of examination of the blood in rickets continue to be variable, like those of earlier observers. Kaneko (1924) in forty rachitic infants found a slight decrease in the average number of erythrocytes and of polymorphonuclear leukocytes; an increase in the number of small lymphocytes and the other counts normal. In 870 cases, Wiltsche (1924) found constant anemia of a variable degree in severe rickets; often also in light cases. Merlini (1926) reported in detail the condition of the blood in thirty rachitic infants, together with an extensive review of the literature. DeVilla and Cartia (1925), in general agreement with previous investigators of the blood in infantile rickets, found a slightly decreased red cell count, the leukocyte count variable (normal or showing variable leukocytosis or sometimes leukopenia), lymphocytosis constant (allowance being made, however, for the normal lymphocytosis of infants), the number of eosinophils usually normal or below, immature granulocytes frequent and sometimes nucleated reds. The observations were correlated with those on smears from the bone marrow, as has been mentioned. Stransky and Wittenberg (1926) concluded that infantile anemia is due to hypofunction of the bone marrow, with a decreased number of red and white cells and platelets. When anemia occurs during rickets, the examination of the blood helps to indicate the stage and the severity of the rickets, and the blood improves parallel with the general recovery on antirachitic treatment. Baumann (1928) ascribed the anemia to lack of iron.

In rachitic rats, Maurer and his associates (1925) found but little change in either the total or the differential leukocyte count. But the constant appearance of erythroblasts in the blood after from three to five weeks and of myelocytes after seven weeks indicates the involvement of the bone marrow. Sherif and Baum (1927) did not find any significant changes in the hemoglobin content or the erythrocyte count of rachitic rats. They observed, however, a marked thrombopenia, which occurred likewise during a dietary deficiency of vitamin A, but not during a deficiency of vitamins B and C.

**Spleen and Lymph Nodes:** In rachitic puppies, Davies (1923) noted hyperplasia of the lymphoid tissue in the spleen and the lymph nodes. Giant cells were fairly numerous. Wilsche (1924) found splenic enlargement in all anemic rachitic infants (29 per cent of 870 rachitic infants). The lymph nodes (inguinal, axillary and cervical) were enlarged in about the same percentage of cases, but Wilsche ascribed this enlargement to causes other than the rickets.

**Gonads and Endocrine Organs:** In young rats with rickets (complicated by a deficiency of vitamin A), Eckstein (1923) found a marked atrophy of the testis and degeneration of the seminiferous tubules with a failure of spermatogenesis. The ovaries were more resistant and appeared normal in structure, although conception did not occur.

According to Davis (1923), the most striking change in rachitic puppies, aside from the lesions of the bones, was in the thyroid gland. The follicles were enlarged and filled with colloid. It has long been known that enlargement of the parathyroids occurs in rachitic rats (Erdheim) and in infants (Ritter). A similar parathyroid hypertrophy in rachitic chickens was recently observed by Doyle (1925) and Nonidez and Goodale (1927). The latter authors found that the enlargement involved both hypertrophy and hyperplasia of the parenchyma cells. Later there is a phase of regression, in which the epithelial cell cords appear shrunken, but this may coincide with hyperplasia of the stroma. In some cases, the parathyroid glands showed localized degenerative changes, mucoid or keratinous, of doubtful significance.

*(To be Concluded)*

## Notes and News

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**University News, Promotions, Resignations and Appointments.**—Claude H. Forkner and Leone McGregor have been granted fellowships for the study of pathology by the medical fellowship board of the National Research Council.

The following announcements effective July 1, have been made by the University of California Medical School: Isabel H. Perry has been appointed instructor in pathology; A. M. Moody, instructor in pathology, and S. R. Mettier, assistant professor of medicine and pathology (absent on leave 1929-1930). Z. E. Bolin was promoted from instructor in pathology to assistant professor of pathology, and J. F. Rhinehart from assistant in pathology to instructor in pathology.

Stuart Graves, dean and professor of pathology, University of Alabama School of Medicine, gave the Alpha Omega Alpha lecture at Augusta, June 1, on "Relationship between Premedical Education and Medical Education," and on June 3 addressed the graduating class on "American Medicine and Young Graduates."

Arthur T. Delaney has resigned his fellowship for work in pathology under the medical fellowship board of the National Research Council to accept the position of pathologist to the Englewood Hospital, Chicago.

William H. Welch has resigned as a member of the state board of health of Maryland after a continuous service of thirty-one years; Thomas S. Cullen succeeds Dr. Welch.

Germanus J. France, Baltimore, has been appointed automobile coroner according to a new law that provides for a separate coroner to investigate deaths caused by automobile accidents.

William D. Collier has been made director of the department of pathology and has been promoted to a full professorship at the St. Louis University School of Medicine.

George H. Whipple, professor of pathology in the University of Rochester, has been elected member of the National Academy of Sciences.

Theobald Smith has retired from the directorship of the department of animal pathology of the Rockefeller Institute for Medical Research, and Carl Ten Broeck is now acting director.

Nathan C. Foot, professor of pathology, University of Cincinnati College of Medicine, will spend a sabbatical year of study abroad, returning in the fall of 1930.

Leon H. Collins, Jr., who has been working in biochemistry and pathology under the medical fellowship board of the National Research Council, has accepted a position in the department of pharmacology in the University of Pennsylvania.

Eugene L. Opie, Philadelphia, has been awarded the Trudeau Medal of the National Tuberculosis Association for his work on tuberculosis in childhood.

Eugene C. Woodruff, who has been working in pathology at Vanderbilt University under the medical fellowship board of the National Research Council, has accepted a position in the department of pathology at Vanderbilt.

Mary Stevenson has been appointed assistant in pathology and Clyde W. Holland has taken the chair of bacteriology at Dalhousie University, Nova Scotia.

**Society for Experimental Biology and Medicine.**—The newly elected officers are: president, Peyton Rous; vice president, David Marine; secretary-treasurer, A. J. Goldforb; councillors, F. P. Gay and G. B. Wallace.

**Federation of American Societies for Experimental Biology.**—The meeting this year will be replaced by that of the Thirteenth International Physiological Congress in Boston, from Aug. 19 to 23, 1929. There will be no scientific



session of the societies of the federation as such, but the usual business meetings of the federated societies will be held on August 19, prior to the opening session of the congress.

**Fellowships and Scholarships in the Medical Schools of the United States and Canada.**—The second part of the *Journal of the Association of Medical Colleges*, vol. 4, no. 2, April, 1929, gives an authoritative list of fellowships and scholarships available in the medical schools of the United States and Canada.

**Reduction in Price of Biography of T. Mitchell Prudden.**—It will be of interest to pathologists to note that the price of "Biographical Sketches and Letters of T. Mitchell Prudden," pioneer American pathologist and professor of pathology in the College of Physicians and Surgeons, Columbia University, from 1892 to 1909 (pages 311, New Haven, Conn., The Yale Press), has been reduced to \$2 a volume.

**Endowment of Fellowships.**—The Lucius N. Littauer Foundation has made a grant of \$50,000 to Albany Medical College for three research fellowships, two in pathology and one in physiology and medicine.

**International Congress of Microbiologists.**—The meeting which was to be held at the Pasteur Institute in Paris in October, 1929, has been postponed until June, 1930. American microbiologists are invited to take part in the congress.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

THE EFFECT OF BILE SALTS UPON UTERINE CONTRACTIONS AND UPON THE ACTION OF PITUITARY EXTRACT. J. HOFBAUER, *Am. J. Obst. & Gynec.* **16**: 245, 1928.

The effect of bile salts and their interaction with pituitary solution on the uterine muscle in the guinea-pig were studied. The experiments were made by kymographic readings of the contracting uterine horn in 50 cc. of Locke's solution. Diluted pituitary solution was added, and after its effect was demonstrated one-fourth strength sodium glycolate was added. A suppression of the spontaneous uterine contractions followed, with a loss in muscle tone. It then took a much greater amount of pituitary solution to restore the uterine contractions and tone. In the pregnant uterus the bile salts had less effect and the muscle was more sensitive to the action of pituitary solution. This was most pronounced as full term was approached. The increase in the bile acid content of the blood during pregnancy has been demonstrated by others. This apparently holds the uterus in obedience and tolerance to its increase in size. At term, when the uterus has become more sensitive, the suppressing power of bile salts is overcome by the hypophyseal secretions which have then become demonstrably increased.

A. J. KOBAK.

THE FEMALE SEX HORMONE. R. T. FRANK, M. D. GOLDBERGER and L. C. MCGEE, *Am. J. Obst. & Gynec.* **16**:387, 1928.

The vaginal spread test in the rodent is specific for the female sex hormone; and testicular extracts do not give a positive vaginal spread test when injected into castrated rats or mice.

A. J. KOBAK.

SUPRARENAL INSUFFICIENCY. L. C. WYMAN, *Am. J. Physiol.* **87**:29 and 42, 1928.

The lethal intraperitoneal dose of histamine acid phosphate for normal rats, and for those in which single suprarenalectomy had been performed was found to be over 100 mg. per hundred grams body weight. In animals in which double suprarenalectomy has been performed, it was diminished to about 7 mg. per hundred grams of body weight. This increased susceptibility persists unchanged for at least five months after operation. The presence of accessory cortical tissue, or of cortical transplants, did not affect this increase of susceptibility, while the presence of accessory chromaffin tissue appeared to afford protection. Complete or partial protection from fatal doses was also conveyed by the intraperitoneal injection of small doses of epinephrine hydrochloride. It is concluded that as the increase of susceptibility appears to be due to lack of medullary tissue, to the extent that it is valuable as a test of suprarenal function, it concerns that of the medullary rather than the cortex.

In rats, previous thyroidectomy was found not to affect the symptoms, the mortality rate, the susceptibility to diphtheria toxin and the susceptibility to histamine intoxication of suprarenalectomized animals. It was found that the intraperitoneal injection of from 6 to 10 cc. of 5 per cent dextrose solution may cause the death of suprarenalectomized animals, while such dosage is without effect on normal animals. In animals on which operation had been performed, smaller doses did not affect the increased susceptibility to histamine intoxication, and apparently not that to diphtheria toxin. In rats it would appear that dehydration is not an important factor in suprarenal insufficiency.

H. E. EGGERS.

THE UTILIZATION OF ACETOACETIC ACID BY NORMAL AND DIABETIC DOGS BEFORE AND AFTER EVISCERATION. I. L. CHAIKOFF and S. SOSKIN, *Am. J. Physiol.* **87**:58, 1928.

Sodium aceto-acetate injected intravenously into normal and eviscerated dogs disappears rapidly. Since there are not sufficient acetone bodies in the tissues several hours after the injection to account for the amount injected, it would appear that aceto-acetic acid can be utilized by muscle. In depancreatized dogs the aceto-acetic acid disappears more slowly, while in eviscerated diabetic dogs the disappearance takes place in the normal time. It is concluded that the excessive appearance of the acetone bodies in the tissue fluids of diabetic animals is not due to diminished utilization of them by the animal.

H. E. EGGERS.

THE RÔLE OF THE ANTERIOR PITUITARY IN HASTENING SEXUAL MATURITY IN RING DOVES. O. RIDDLE and F. FLEMION, *Am. J. Physiol.* **87**:110, 1928.

In a study of the effect on precocious sexual maturity in immature doves, it was found that daily anterior pituitary homeotransplants increased testicular growth, while a similar, but less marked, effect was obtained in some cases with ovarian growth. Similar effects were obtained by the intraperitoneal administration of a glycerin extract of fresh bovine anterior lobes. Body weight was not affected or was adversely affected. With the glycerin extracts, there was frequent enlargement of thyroids, livers and spleens.

H. E. EGGERS.

EFFECTS OF DIFFERENT FOOD SUBSTANCES UPON EMPTYING OF THE GALL-BLADDER. W. F. KRAUSE and L. R. WHITAKER, *Am. J. Physiol.* **87**:172, 1928.

In cats, fats and fatty acids were by far the most active foods in emptying the gallbladder, the unsaturated fatty acids being apparently more active than the saturated. Pure carbohydrates had little or no effect, and proteins only a slight effect.

H. E. EGGERS.

MUSCLE HEMOGLOBIN CONCENTRATION DURING GROWTH AS INFLUENCED BY DIET FACTORS. G. H. WHIPPLE, A. H. GROTH and F. S. ROBSCHT-ROBBINS, *Am. J. Physiol.* **87**:185, 1928.

Litter-mated pups were fed on an adequate synthetic bread ration, or on a bread ration to which were added large amounts of cooked liver. After ten weeks' feeding there were no noteworthy differences in the concentration of muscle hemoglobin in the animals on the two diets. After from fifteen to twenty weeks on these diets, the pups which were fed liver showed a distinct increase both in blood hemoglobin and in the concentration of muscle hemoglobin. In contrast with the levels of blood hemoglobin, those of muscle hemoglobin are stable and are not easily disturbed. The maintenance factor required to replace the wear and tear of muscle hemoglobin is unknown.

H. E. EGGERS.

WATER RETENTION UNDER LOW BAROMETRIC PRESSURE. C. S. SMITH, *Am. J. Physiol.* **87**:200, 1928.

In dogs and rats kept under atmospheric pressures reduced from 2.6 to 9.8 cm. of mercury, water retention was observed. This retention was accompanied by restlessness, and it is suggested that this mechanism is concerned in the reaction by many animals and some human beings to approaching weather changes.

H. E. EGGERS.

COAGULATION TIME IN PARATHYROID TETANY. J. C. BROUGHER, *Am. J. Physiol.* **87**:221, 1928.

In parathyroidectomized dogs, there was a delay in blood clotting time during tetany varying from a few seconds to over thirty hours. The administration of

1 ounce (28.35 Gm.) of cod liver oil, or 0.4 cc. of acterol, restored clotting time to normal after a period of from two to four hours. If these were given for from twenty to forty days, the animals recovered, and their blood coagulation and serum calcium returned to normal.

H. E. EGGERS.

STUDIES IN THE DIGESTION OF LECITHIN BY PANCREATIC ENZYMES. SIDNEY A. PORTIS, J. A. M. A. **91**:1248, 1928.

Normal duodenal contents digest lecithin and gastric contents do not. In patients with cardiac decompensation there is a definite depression of enzyme activity as far as lecithin digestion is concerned. There is no apparent alteration in pancreatic enzyme activity in normal pregnant women. The pancreatic enzyme activity is depressed in the untreated duodenal ulcer and returns to nearly normal with the administration of alkalis. Patients with ulcers treated by the ordinary methods of rest in bed and food and without the administration of alkalis did not show a return to normal in the third week of management.

AUTHOR'S SUMMARY.

THE PHYSIOLOGICAL RESPONSE OF RABBITS TO INSULIN. M. SAHYUN and N. R. BLATHERWICK, J. Biol. Chem. **79**:443, 1928.

The rate at which sugar can be mobilized from the liver is an important factor in the determination of the responsiveness of an animal to the hypoglycemic action of intravenously injected insulin. Rabbits maintained on a diet rich in carbohydrates are markedly refractive. Rabbits whose reserve of sugar-yielding glycogen is, on the contrary, depleted, or cut off from mobilization as the result of splanchnectomy, are markedly responsive. More insulin is required to produce convulsions when given intravenously than when administered either subcutaneously or intraperitoneally.

ARTHUR LOCKE.

THE ENERGY EXCHANGE IN OBESITY. J. M. STRANG and F. A. EVANS, J. Clin. Investigation **6**:277, 1928.

Observations were made on eight obese women, normal except for excess weight, who were reducing by measures of diet alone. The basal metabolism was determined at intervals of a few days to two weeks. In seven patients with normal metabolism, the increase in calories was 26 per cent above normal for the same persons if of ideal weight. This was not proportional to the weight excess, but was proportional to the increase of body surface. On reduction of weight, the caloric value dropped to 6 per cent above normal, even when the body weight remained 40 per cent above normal.

H. R. FISHBACK.

RENAL FUNCTION IN CHRONIC CARDIAC DISEASE WITHOUT SIGNS OF HEART FAILURE. H. J. STEWART and J. F. McINTOSH, J. Clin. Investigation **6**:325, 1928.

In thirty-five patients recently recovered from heart decompensation, renal function was tested by the following methods: (1) the urea concentration index; (2) the phenolsulphonphthalein test; (3) the concentration test, and (4) the dilution test. In ten patients, all four tests gave normal values. The urea concentration index was normal in all except eight patients, and the phenolsulphonphthalein excretion was subnormal in only one patient. The dilution test showed lessened water excretion, failure of the specific gravity to fall or both in seventeen patients, while ten patients showed diminished concentration power. Thus, the most frequent abnormality found was more or less fixation of the specific gravity of the urine. After the age of 30, or in patients with arteriosclerosis or hypertension, normal renal function was rarely found. There was no correlation between the duration of heart disease and the degree of impairment of renal function.

H. R. FISHBACK.

PROPERTIES OF THE GONADS AS CONTROLLERS OF SOMATIC AND PSYCHICAL CHARACTERISTICS. CARL R. MOORE, *J. Exper. Zool.* **50**:455, 1928.

By surgical removal of the testis from its epididymis in rats and guinea-pigs, the life and motility of spermatozoa remaining in the isolated epididymis have been studied under a variety of conditions.

In the isolated epididymis of the guinea-pig (opposite testis normal), spermatozoa remain alive and capable of motility on proper stimulation for seventy days, but with double epididymal isolation (both testes removed) this capacity for motility persists for but twenty-three days. In the rat comparable time intervals are thirty days and seventeen days. The greater length of life of spermatozoa when one testis is present, in contrast with the absence of all testis tissue, becomes an indicator for the presence of the testis hormone, since it follows under conditions when no spermatogenesis is present. This spermatozoon-motility test provides a dependable, easily read, purely objective test for the testicular hormone.

The temperature regulating influence of the scrotum is easily demonstrated by confining the isolated epididymis in the abdomen; the length of life of the spermatozoa under such conditions is greatly shortened.

The spermatozoon-motility test has been studied under such a variety of conditions as the following: as influenced by (1) early and later experimental cryptorchid testes; (2) macerated testis injections; (3) delayed removal of the testis hormone; (4) nonliving testis grafts; (5) living testis fractions.

The physiology of the epididymis has likewise been recognized in a new light.

AUTHOR'S SUMMARY.

A STUDY OF THE ADRENAL CORTX IN THE MOUSE AND ITS RELATION TO THE GONADS. R. DEANESLY, *Proc. Roy. Soc., London* **103**:523, 1928.

The histologic difference between the suprarenal glands of male and female mice, reported by previous writers, has been further investigated. At the age of 3 weeks, the suprarenals are alike in the two sexes; in inner dark-staining cortical zone can be distinguished. Growth of this zone ceases in the male before the age of 5 weeks; a small amount of degeneration takes place, and fibrous reticular tissue develops around the medulla. In the female, this zone continues to grow until puberty; it then occupies more than half the cortex. Later, it degenerates slowly in the unmated animal, and normally disappears before the end of the reproductive period. The reduction of this zone is accompanied by a proliferation of fibrous tissue in the same region which persists after total degeneration has taken place. No correlation has been found between histologic changes in the gland of the unmated mouse and the estrual cycle. Complete degeneration of the inner zone of the cortex takes place between the seventh and twelfth days of pregnancy; the histologic changes occur more rapidly than those in the gland of the unmated female, but are otherwise identical with them. A new inner zone may arise later in the cortex; this, though similar to the earlier one, is distinguishable from it, but is also of a transitory character. The effect of castration on the suprarenal gland is to cause the growth of an inner cortical zone of the female type. Ovariectomy appears to have no effect on the suprarenal gland. The histology of the suprarenals in mice is discussed in relation to that of man and other mammals. Double suprarenalectomy was performed on a number of male and female mice which bred normally after the operation. It was found that the estrual cycle was slightly lengthened in unmated suprarenalectomized females, but otherwise was normal.

AUTHOR'S SUMMARY.

THE PHYSIOLOGY AND PHARMACOLOGY OF THE UMBILICAL CORD CIRCULATION. H. RUNGE, M. BAUER and H. HARTMANN, *Arch. f. Gynäk.* **134**:626, 1928.

Perfusion studies were carried on in portions of the placenta and the umbilical cord to obtain information regarding the physiologic and physiochemical part played by the cord circulation. The difference in the pressure of the arteries and the vein

of the umbilical cord amounted to about 50 per cent. The blood pressure of the cord vein was, nevertheless, higher than that of the somatic veins of the fetal body which is based on the mechanical power of the fetal heart. The umbilical vein is permeable to aqueous stains but not to colloidal stain material. The permeability increases with the proportion of pressure utilized. Neither aqueous nor colloidal stains could be filtered through the arteries. The relation of the permeability of the veins to the origin of the amniotic waters was then significantly discussed. The anatomic verification of the vessel permeability was found in the relationship of the surrounding Wharton jelly of the cord to the vein and arteries. The vein was intimately related to its surrounding substance, whereas this is more or less lacking in the umbilical arteries.

A. J. KOBAK.

SUDDEN DEATH FROM VENTRICULAR FIBRILLATION. W. STEPP and G. W. PARADE, München. med. Wchnschr. **75**:1869, 1928.

Air in quantities of from 0.5 to 30 cc. of suspended carbon and oil, some emulsified, was injected into the left ventricle of dogs. There followed marked restlessness, dyspnea, rapid breathing and severe disturbances of the heart rhythm. Marked changes occurred in the electrocardiograms. Although ventricular flutter and fibrillation were noted, auricular fibrillation was not observed. Continuous ventricular fibrillation always occurred within seven minutes, but usually appeared within two or three minutes following the injection. In all experiments, the onset of ventricular fibrillation appeared from one half to one minute before respiration ceased. In the experiments without ventricular fibrillation, especially following air embolism, the death of the heart was slower and preceded by extrasystole and sinus tachycardia. The postmortem examination confirmed the results of Gundermann, in all experiments with ventricle fibrillation, i. e., a massive accumulation of air bubbles or carbon particles in the coronary arteries. Air bubbles and carbon particles were distributed also in the arteries of the brain and elsewhere. The presence of air or carbon particles in the coronary arteries, demonstrated in all experiments in which death resulted from ventricular fibrillation, leads to the conclusion that ventricular fibrillation is caused by a disturbance of the blood supply of the myocardium or of the conduction system. Certain clinical applications are discussed in conclusion.

EDWIN F. HIRSCH.

### Pathologic Anatomy

ANEURYSM OF THE SPLENIC ARTERY. E. L. HUNT, Am. J. M. Sc. **176**:195, 1928.

A case of this rare condition is described with autopsy observations. Besides the ruptured aneurysm, there were also arteriosclerosis, cardiac hypertrophy and pulmonary edema.

PEARL ZEEK.

ADDISON'S DISEASE IN THE NEGRO. L. S. EVANS, Am. J. M. Sc. **176**:499, 1928.

This disease in negroes is probably more common than is generally supposed, but is difficult to diagnose because of the natural pigmentation of the skin. Three cases are reported, one with autopsy observations.

PEARL ZEEK.

AN EXPERIMENTAL STUDY OF ARTERIAL COLLATERAL CIRCULATION. H. E. PEARSE, JR., Ann. Surg. **88**:227, 1928.

The author removed the main portion of the femoral artery in dogs and found that gangrene did not develop, nor was there any functional disability. With the adoption of Hill's injection method, a rich anastomosing vascular network could be demonstrated in these limbs. Sections of the tissue did not reveal newly formed blood vessels. The presence of one or two lateral branches will prevent total atrophy of a segment of artery isolated between ligatures, and three or more will preserve such a segment intact. Vasa vasorum pass around the ligature, obstructing their artery and thus acting as collateral channels.

N. ENZER.

PRIMARY BILATERAL TUMORS OF THE TESTICLE. C. C. HIGGINS, *Ann. Surg.* **88**:242, 1928.

The author reports a case of bilateral primary embryoma of the testes.

N. ENZER.

MORPHOLOGICAL CHANGES IN EXOPHTHALMIC GOITER FOLLOWING THE USE OF LUGOL'S SOLUTION. C. ALEXANDER HELLWIG, *Surg. Gynec. Obst.* **47**:173, 1928.

Thirty exophthalmic goiters removed after Plummer's treatment were compared with thirty glands removed without previous iodine medication. Most of the observations described by Rienhoff could not be confirmed. After Plummer's treatment no changes in the vascularity and in the amount of fibrous tissue were found. The acini were neither round, smooth-walled nor of regular size and form. Neither was the epithelium flat or cuboidal nor were the nuclei small, irregular and pyknotic. A formation of adenoma-like tumefactions and colloid cysts visible with the unaided eye did not occur in the material. In 84 per cent of the glands removed after Plummer's treatment, the only definite difference, as compared with untreated glands, was found in the appearance of the colloid. The acini of these glands had more and higher concentrated content in spite of the fact that the hyperplastic character of the glands was not altered. These observations corroborate Albert Kocher's observation that most of the exophthalmic goiters removed after iodine medication show distinctly more stained colloid than those without. Therefore, if one regards the liquefaction of the colloid as the most characteristic feature of exophthalmic goiter, it is doubtful that the change in the amount and quality of the colloid which follows Plummer's treatment completely explains the clinical improvement. The fact that in this material there was improvement in four cases following the use of a compound solution of iodine but no appearance of thick colloid in the glands, and that in one case there was no improvement after treatment with iodine but a gland rich in concentrated colloid, suggests that this problem is much more complicated and will not be solved by the anatomic method alone.

AUTHOR'S SUMMARY.

POLYCYTHAEMIA IN THE RABBIT FOLLOWING OPERATIONS INVOLVING THE PERITONEUM. R. HOWARD MOLE, *J. Path. & Bact.* **31**:645, 1928.

Four different kinds of operative procedures involving the peritoneum of the rabbit are reported, carried out under ether or procaine hydrochloride anesthesia, in each of which, after a brief period of anemia, a condition of polycythemia results. The cause of the polycythemia is undetermined.

AUTHOR'S SUMMARY.

CAPILLARY PERMEABILITY IN ACUTE URANIUM NEPHRITIS. CAROLINE WHITNEY, *J. Path. & Bact.* **31**:699, 1928.

The permeability of capillaries is decreased after uranium poisoning. The decreased permeability is evident within from eighteen to twenty-four hours after the administration of the drug; therefore, it is probable that the effect on the capillaries is a direct effect rather than a secondary effect of the kidney degeneration. The state of decreased permeability persists throughout the period in which it is possible to produce edema by the administration of excess fluid.

AUTHOR'S SUMMARY.

THE PRODUCTION OF HYPERPLASIA IN THE ALVEOLAR EPITHELIUM OF THE LUNG OF THE RABBIT. J. S. YOUNG, *J. Path. & Bact.* **31**:705, 1928.

Active manifestations of proliferation in the epithelial cells lining the marginal alveoli of the lung of the rabbit can be produced by the intrapleural injection of an emulsion of liquid paraffin and bile salts, whereas liquid paraffin alone is

ineffective. Similar changes follow the injection of solutions of a variety of neutral salts; viz., sodium chloride, calcium chloride, strontium chloride and aluminum chloride. The epithelial reaction increases as the valency of the cation of the salt increases. The action of calcium ions is not abolished by sodium ions. The significance of physical factors in the genesis of the epithelial proliferation is discussed.

AUTHOR'S SUMMARY.

THE APPEARANCE OF DOUBLY REFRACTING SUBSTANCE IN FORMALIN-FIXED RABBIT'S TISSUES. J. B. DUGUID and J. MILLS, *J. Path. & Bact.* **31**:721, 1928.

Doubly refracting substances make their appearance in the tissues of certain organs, notably the liver, after their removal from the body. The appearance has been investigated in human, rabbit and mouse tissues. Fixation in formaldehyde delays and limits the development of these substances but does not permanently prevent it. No development is found in tissues which have been fixed in corrosive mercuric chloride, U. S. P., or in osmic acid. No development takes place in tissues which have been fixed in potassium bichromate, and with formaldehyde (formol-Müller) a slight development takes place. The development of the substances is dependent on the tissues being placed in an acid medium after fixation. The substances are considered to be fatty acids, formed by hydrolysis from the lipoids in the tissues. We have not succeeded in staining them. The distribution of the substances gives no reliable indication as to their exact site of origin in the tissues, because in any piece of tissue the distribution alters according to the treatment to which that particular piece of tissue has been subjected. The anisotropic substances which occur in the suprarenal gland were compared with those which develop in the liver. The two substances were found to be similar in their chemical reactions, and considerable evidence pointed to both as being results of postmortem changes in the tissues. Injections of cholesterol into the blood stream of rabbits before death did not affect the appearance or the amount of the doubly refracting substances developing in the livers or other organs of these animals. We conclude that, since doubly refracting substances so readily develop in the tissues after death, their presence is of little importance as evidence of the state of affairs during life.

AUTHOR'S SUMMARY.

BLOOD CHANGES AFTER SPLENECTOMY IN SPLENIC ANAEMIA, PURPURA HAEMORRHAGICA AND ACHOLURIC JAUNDICE, WITH SPECIAL REFERENCE TO PLATELETS AND COAGULATION. W. HOWEL EVANS, *J. Path. & Bact.* **31**:815, 1928.

In ten of eleven cases in which splenectomy had been performed, the platelets showed a considerable increase. In one case of purpura hemorrhagica, they failed to show any marked increase, while in one case of splenic anemia (Rosenthal's thrombocythemic type) they rose to a high level, which was persistently maintained until the death of the patient from mesenteric thrombosis. The clotting time showed a rough parallelism to the platelet level. The clot retraction seemed much more proportional to the platelet count. After splenectomy there seems to be no correlation between the immediate and transient rise of the granular leukocytes and the slower and more persistent rise of the platelets.

AUTHOR'S SUMMARY.

THE RELATION OF THE BLOOD PLATELETS TO THROMBOSIS AFTER OPERATION AND PARTURITION. R. Y. DAWBARN, F. EARLAM and W. HOWEL EVANS, *J. Path. & Bact.* **31**:833, 1928.

After operations and childbirth, and especially after cesarean section, the number of platelets in the blood begins to rise about the fourth day, increases to a maximum about the tenth day and thereafter falls slowly to the normal level. A diminution of platelets is associated with an increase, and an excess of platelets



with a shortening of the blood coagulation time. The time relations of clinical thrombosis and embolism are similar to those of the platelet reaction: they are most frequent about the tenth day after operation or childbirth. The platelets show no change after simple hemorrhage, anesthesia or stopping in bed and no constant variation in sepsis. The platelet reaction is excited by fractures, and a similar rise occurs during convalescence from acute lobar pneumonia. It is suggested that the feature which is common to the various stimuli which have been identified is tissue injury and the absorption of break-down products.

AUTHOR'S SUMMARY.

BONE-MARROW IN THE SUPRARENAL GLAND. K. KNABE, *Centralbl. f. allg. Pathol. u. path. Anat.* **43:57**, 1928.

In a woman, aged 75, dying of cardiac failure, a red-brown nodule, 7 by 6 mm., was found in the cortex of the right suprarenal gland at autopsy. The mass was soft and sharply circumscribed, and on histologic examination all stages of erythropoiesis and giant cells of the type found in marrow were seen in it. Three possible explanations are offered for the anomaly. First, a compensatory new formation of marrow; second, the development of marrow carried to the suprarenal gland by the blood stream, and third, a congenital heterotopy of marrow.

GEORGE RUKSTINAT.

THE LIPOIDS OF THE MYOCARDIUM. E. SEHRT, *Centralbl. f. allg. Pathol. u. path. Anat.* **43:97**, 1928

A wide discrepancy exists in the results obtained by pure chemical and histochemical investigations of the cardiac lipoids. These lipoids are known to consist of about 20 per cent fats found for the most part in the intermuscular tissues, 0.07 per cent cholesterol esters and from 60 to 70 per cent unsaturated phosphatides. The latter are labile and do not stain by the ordinary methods. Five factors influence the results of staining: (1) the affinity of the stain for its solvent (alcohol); (2) the solubility of the lipoids in this solvent; (3) the solubility of the stain in the examined lipoids; (4) the question if the affinity of the sudan III for its solvent is greater or less than its affinity for the lipid; (5) physicochemical combinations of fat with other bodies, such as water, which prevent the combination of the stain with the lipid. From this it follows that a lipid can be stained if it is not soluble in the histologic solvent and if the affinity of the sudan III is greater for the lipid than for its own solvent. The method advocated to secure the best results is as follows: Thin frozen sections are cut from fresh tissue, dipped into distilled water and dried in air for one hour. Staining is then carried out in an alcohol acetone solution of sudan III for from two to three hours. After this the sections are quickly shaken in 65 per cent alcohol, washed in distilled water, counterstained in Delafield's hematoxylin, washed in water and embedded in glyceringelatin on a slide. By this method, the cardiac muscle is seen to be packed with fat droplets in both the longitudinal and the cross-striations. In addition, fine fibrillae can be seen connecting the fat droplets.

GEORGE RUKSTINAT.

CORPORA ARENACEA IN THE LUNG. D. HUSSEINOFF, *Centralbl. f. allg. Pathol. u. path. Anat.* **43:481**, 1928.

A man, aged 30, dying of sepsis and malarial coma, at autopsy had an extensive right fibrous pleuritis and in the center of the right lower pulmonary lobe a red, stony mass, the size of a hazelnut. In this were bodies resembling corpora amylacea, some of which were partially calcified. The vessels in the mass were involved in various stages of thickening and hyalinization, and those completely obliterated and occupied by concentric calcium deposits were regarded as corpora arenacea.

GEORGE RUKSTINAT.

FAMILIAL CONGENITAL MACROSOMIA ADIPOSA. T. CHRISTIANSEN, *Hospitals-tidende* **71**:421, 1928.

Christiansen discusses the endocrine disorder designated by this name, seen in the children of two sisters with menstrual anomalies. Of nine children born at term, seven had macrosomia, five dying within the first year. Necropsy revealed adenomas in the suprarenal cortex and eosinophilia in the thymus. Congenital macrosomia is regarded as a suprarenal syndrome belonging to the obese type (Guthrie and Emery), due to a hyperepinephry (Apert), but distinguished by the absence of hirsuties and genital changes and in other ways from the suprarenal syndromes described in the literature to date.

THE CONNECTION BETWEEN THE HYPOPHYSIS AND THE MID-BRAIN. B. N. MOGILNITZKY, *Virchows Arch. f. path. Anat.* **267**:263, 1928.

The author exposed the brains of three dogs to roentgen rays, and found in all, besides atrophy of the glandular portion of the hypophysis, marked proliferation of glia cells and atrophy of the posterior lobe, also bilateral atrophic and degenerative changes in the nucleus supra-opticus and in the tuber cinereum. Degeneration of the tractus supraopticohypophyseus had apparently occurred as a result of the changes in the hypophysis.

B. R. LOVETT.

CHRYSOSIS IN RABBITS AND DOGS. H. BORCHARDT, *Virchows Arch. f. path. Anat.* **267**:272, 1928.

After injection of a gold preparation by various routes into animals, the metal could be demonstrated in bound form in all the organs. It was stored chiefly in the reticular cells of the liver and spleen, and was excreted through the kidneys. Metallic gold could also be demonstrated chemically in the cells after injection of a fine emulsion of the metal.

B. R. LOVETT.

MALFORMATION OF THE LEFT VENTRICLE. H. O. KLEINE, *Virchows Arch. f. path. Anat.* **267**:281, 1928.

After reviewing the literature, Kleine describes his case, in which a band was found resembling one of the chordae tendineae extending from the valve of the foramen ovale to the free border of the mitral valve between the two leaflets. It appeared to be a prolongation of the flap covering the foramen ovale. There were also three, instead of two, pulmonary veins.

B. R. LOVETT.

STENOSIS OF THE CONUS ARTERIOSUS AS A RESULT OF PARIETAL ENDOCARDITIS. G. LEITMANN, *Virchows Arch. f. path. Anat.* **267**:290, 1928.

Stenosis of the conus arteriosus was found following a mural endocarditis with fibrosis of the right ventricle.

B. R. LOVETT.

MALFORMATIONS OF THE ORGANS OF RESPIRATION. F. PAUL, *Virchows Arch. f. path. Anat.* **267**:295, 1928.

Three instances of malformations are described. In the first, the left lung was lacking and the pleural cavity was entirely filled by the pericardium and right lung. A rudimentary lung was attached to the esophagus. In the second case, an artery branched off from the aorta just above the diaphragm, and entered the lower lobe of the left lung. Its branches anastomosed with the left pulmonary artery. Extensive caseous tuberculosis was present, confined to the region supplied with blood from the aorta. The third case, that of a stillborn infant, revealed the upper end of the esophagus ending blindly, and the lower end attached to the trachea at the bifurcation. All three are attributed to a fault in the segmentation process, during the development of the lung from the foregut in early embryonic life.

B. R. LOVETT.

AN AMNIOGENOUS MALFORMATION OF THE SKULL-AND BRAIN. F. FRITSCHKE, Virchows Arch. f. path. Anat. **267**:318, 1928.

In a stillborn infant, the calvarium was lacking, and the hemispheres consisted of two small rudimentary nodules. There were adhesions between the placenta and the right hemisphere, and also two bands which caused a split in the face and a deformity of the left arm. "Very little amniotic fluid" was reported at the birth.

B. R. LOVETT.

PATHOLOGIC HISTOLOGY OF THE CHOROID PLEXUS: I. ALTERATIONS WITH AGE. E. VON ZALKA, Virchows Arch. f. path. Anat. **267**:379, 1928.

## II. ALTERATIONS IN DISEASE, *ibid.*, p. 398.

Even under normal conditions, the epithelium of the choroid plexus may be many-layered and show extensive desquamation. The changes most frequently found are those connected with advancing age. These are: in the epithelial cells, vacuolization, pigmentation and flattening; in the connective tissue, diffuse and focal sclerosis, formation of cysts, psammomas and hyaline bodies, and calcification. These physiologic alterations must be considered before attributing changes to disease of the nervous system.

Marked hyperemia of the choroid plexus was found in a variety of conditions. Amyloid occurred as a part of general amyloidosis. Inflammatory changes, investigated chiefly in tuberculous meningitis, consisted of infiltration of the blood vessel walls and perivascular connective tissue with lymphocytes, epithelioid cells, leukocytes, occasional giant cells and nets of fibrin. Fibrinopurulent exudate was found between the villi in several cases. Leukocytic infiltration occurred in two cases of suppurative meningitis. In chronic inflammation, especially syphilis, there was increase of connective tissue around the vessels, with infiltration of plasma cells and lymphocytes. In leukemias the capillaries were seen to be distended with the corresponding type of cell. Tumors of the plexus are rare; one instance of benign papilloma was investigated. A connection between uremia and changes in the plexus is denied by the author, since the changes reported by others and found by him were largely increase in hyaline connective tissue, such as occurs physiologically with advancing age. No characteristic changes were associated with diabetic coma.

B. R. LOVETT.

INNERVATION OF THE VOLUNTARY MUSCLES. T. TSUNODA, Virchows Arch. f. path. Anat. **267**:413, 1928.

Different types of nerve-endings in the voluntary muscles were examined by a special staining method and described. The results indicated a double or triple efferent innervation of the muscle. Section of the nerve roots above the spinal ganglion was followed by wallerian degeneration of the medullated fibers, and no change in the nonmedullated ones. In the muscle bundle itself, half of the medullated nerve-endings degenerated while the other half remained intact. Section below the ganglion caused degeneration of all medullated nerve-endings. The author concludes that half of the medullated nerves are motor while the other half belong to the sensory nerves of the spinal ganglion. In beriberi in pigeons, marked degeneration of the axis cylinder of the nerve-endings was invariably found, swelling followed by atrophy. In nonmedullated fibers the changes were much less pronounced. Giving vitamin B improved the condition.

B. R. LOVETT.

CHANGES IN THE NERVE-ENDINGS OF THE SKIN IN BERIBERI IN BIRDS. T. TSUNODA and N. KURA, Virchows Arch. f. path. Anat. **267**:421, 1928.

In pigeons and ducks with beriberi, changes in the axis cylinders of the sensory nerves and their endings are in general those of cloudy swelling. Frag-

mentation or granular degeneration is not found. When one injects vitamin B into these animals, the clinical symptoms disappear. The sensory nerve-endings as well as the motor nerves return to the normal condition rapidly, within twenty-four hours. One may conclude that disturbances of the motor, sensory and sympathetic nerves go together in beriberi. The histologic changes in motor and sensory nerves are the same.

B. R. LOVETT.

## Pathologic Chemistry and Physics

BLOOD CHEMICAL STUDIES IN ARTERIAL HYPERTENSION. RALPH H. MAJOR, *Am. J. M. Sc.* **117**:188, 1929.

In certain cases of hypertension, the blood is found to contain an increased amount of some substance giving the same color response as guanidine and having certain chemical properties like those exhibited by the guanidine bases.

PEARL ZEEK.

THE REACTION OF HUMAN BILE AND ITS RELATION TO GALL STONE FORMATION. JOHN G. REINHOLD and L. KRAAER FERGUSON, *J. Exper. Med.* **49**:681, 1929.

The human gallbladder acidifies the bile. In this respect its action is similar to that of the gallbladder of lower animals, previously described by other workers. The hydrogen ion concentration of gallbladder bile is increased considerably in cases of obstruction of the common or cystic ducts. The highest values were found following complete obstruction. The occurrence of gallstones was not associated with a consistent change in the hydrogen ion concentration of the gallbladder bile.

AUTHORS' SUMMARY.

GASTRIC SECRETION AND URINARY REACTION. DANIEL DAVIES, *Brit. J. Exper. Path.* **10**:1, 1929.

In cases of true achlorhydria the reaction of the urine is remarkably constant, and may afford not only an additional means of diagnosing the condition but may aid in distinguishing between true and false achlorhydria.

PEARL ZEEK.

THE PHOSPHORUS CONTENT OF THE BLOOD IN DIABETES MELLITUS. F. B. BYROM, *Brit. J. Exper. Path.* **10**:10, 1929.

In severe untreated diabetes and in diabetic coma there is a pronounced fall in the organic acid-soluble phosphorus of the blood corpuscles, which appears to be the result of acidosis. After satisfactory treatment by dietetic restriction and insulin, the ester phosphorus returns to the normal level. In fatal diabetic coma the inorganic phosphate rises considerably, probably as the result of renal damage.

PEARL ZEEK.

HYDRAULIC ACTION OF TISSUE FLUID. R. BENEKE, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:166, 1927.

Beneke discusses at considerable length the rôle of the physico-mechanical action of tissue fluid in the normal and pathologic formation of connective tissue. Since water is inelastic and noncompressible, the tissue fluid has the property of transmitting to the cells embedded in the fluid all mechanical impulses and shocks. Normal mechanical impulses to which the body is constantly subjected are those of the pulse wave and of body movements. The effect of such impulses transmitted to cells suspended in a fluid or semifluid matrix would be to disrupt the cellular elements. The latter are protected against the hydraulic action of the tissue fluid by the collagenous connective tissue fibers which are laid down between the

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cells and which take up and dissipate the shock of mechanical impulses. Beneke takes the teleologic point of view that not only does the connective ground substance protect the cells against shock, but that it is laid down to have this protective action as the result of mechanical impulses. It is thus that he accounts for the formation of normal connective tissue in general and for the special arrangement of the connective tissue of the cardiovascular system and of the dura. He then takes up seriatim a number of pathologic connective tissue overgrowths, which are interpreted as the result of abnormal hydraulic impulses, the purpose of the overgrowths being to protect the surrounding tissues from the abnormal shocks; thickening of the endocardium and of the artery wall; elephantiasis; condensation and fibrillation of the crystalline lens and fibrosis about the auditory labyrinth; thickening of the tunica vaginalis, peritoneum and pleura in hydrocele, ascites and pleural effusion; subependymal gliosis and fibrosis of the choroid plexus in chronic hydrocephalus; the formation of the host capsule about achinococcus cysts; the formation of the fibrous wall of neoplastic cysts; the encapsulation of areas of cerebral softening and hemorrhage. The idea is called on to explain even the formation of tumors of the brain, in the causation of many of which Beneke thinks trauma is a factor; the trauma leads to liquefaction or hemorrhage of brain tissue. If the fibrous capsule, which is formed about the liquefied area as the result of hydraulic shocks transmitted by the fluid, is inadequate to protect the surrounding brain tissue, then a tumor may result from the insult of constantly recurring shocks. Since the article is dedicated to Abderhalden, on the occasion of the latter's fiftieth birthday, the author may be pardoned for likening the formation of connective tissue fibrils in a fluid matrix to the precipitation of fibrin through enzyme action, and for considering the process of protective mechanism akin to the immunity reaction.

O. T. SCHULTZ.

TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY. P. FREUDENTHAL, *Virchows Arch. f. path. Anat.* **266**:640, 1928.

A case is described and explained according to Spitzer's theory of reversion to a phylogenetically older step in the development of the heart.

B. R. LOVETT.

## Microbiology and Parasitology

ANTI-STAPHYLOCOCCIC EFFECTS OF THE INTRA-ARTERIAL INJECTION OF CERTAIN DYES. Z. D. ZAU and F. L. MELENEY, *Ann. Surg.* **88**:961, 1928.

The effect of mercurochrome-220 soluble, gentian violet and acriflavine on tissues and on infection was studied by injection into the aorta and the femoral artery of dogs. In fourteen dogs lesions were produced by hemolytic staphylococci, and there was no evidence that the injection of dye twenty-four, forty-eight and seventy-two hours after the injection of the organisms had any effect on the course of the infections. The work is significant, showing that these dyes may be injected intra-arterially without damage to the arteries, and also because of damage to the kidney and liver when the injections were made intra-arterially in doses from 1 to 16 mg. per kilogram of body weight. It is concluded that the failure of the administration of this dye by way of the arteries to act on the infection implies that an intravenous injection of the same quantity would hardly be efficacious.

N. ENZER.

AN INVESTIGATION OF STREPTOCOCCI ISOLATED FROM THE ALIMENTARY TRACT OF MAN AND CERTAIN ANIMALS. J. M. ALSTON, *J. Bact.* **16**:397, 1928.

There is a clearly defined group of organisms sufficiently differentiated to be classified together as enterococci. Like many other bacteria, there are atypical varieties which are intermediate between the typical ones and the closely related varieties. We would specify the attributes which justify the inclusion of an organ-

ism in the enterococcus group as follows: cocci tending to be oval and occurring in pairs or short chains, heat resistant up to 60 C. for ten minutes, and nonhemolytic and capable of fermenting mannitol, as secondary and not invariable characters. Among fifty-one strains of streptococci isolated from the alimentary tract of man, dog and rat, sixteen (31 per cent) conformed to the description of enterococci (Dible). The remainder of the streptococci isolated from feces or intestine, with one exception, grew on a bile-salt medium and were nonmannitol fermenters and heat sensitive, and showed the sugar reactions of *Streptococcus mitis* (Holman). Six streptococci obtained from the mouth or stomach and one obtained from the duodenum did not grow on a bile-salt medium and were of the type of *Streptococcus mitis*, *S. salivarius* or *S. nonhemolyticus III* (Holman).

AUTHOR'S SUMMARY.

ATTEMPT TO CULTIVATE BACTERIA FROM RABBIT ENCEPHALITIS VIRUSES.  
FEI-FANG TANG and M. RUIZ CASTANEDA, J. Bact. **16**:431, 1928.

The experiments failed to show any causal relationship between the ordinary visible bacteria and encephalitis and furnished no evidence to support the suggestion that the filtrable encephalitis virus may change into a true bacterial form.

AUTHORS' SUMMARY.

FILTRATION OF THE VIRUS OF HERPETIC ENCEPHALITIS AND OF VACCINIA.  
HUGH K. WARD and FEI-FANG TANG, J. Exper. Med. **49**:1, 1929.

The virus of herpetic encephalitis and the virus of vaccinia can be demonstrated in the filtrate, if a broth emulsion of fresh tissue containing the virus is passed through a Berkefeld filter.

AUTHORS' SUMMARY.

THE GERMICIDAL AND HEMOLYTIC ACTION OF A-BROM SOAPS. ARNOLD H. EGGERTH, J. Exper. Med. **49**:53, 1929.

The soaps of the a-brom fatty acids are usually more germicidal than the unsubstituted soaps. Only when *B. typhosus* was the test organism was there no increase in germicidal action. For any test organism, germicidal action of the brominated soaps increases rapidly with increasing molecular weight up to a certain point, then diminishes. This is likewise true of the hemolytic titer. The point of maximal germicidal action varies with the different species of test organisms. In the series studied, brominated soaps of 12 and 14 carbon atoms were most germicidal for the gram-negative organisms, while soaps of 16 and 18 carbon atoms were most germicidal for gram-positive organisms. The brominated soaps are, in general, more active in acid than in neutral or alkaline reactions. The reasons for this have been discussed in a previous paper, in which a similar phenomenon with unsubstituted soaps was observed. For certain organisms, the brominated soaps are among the most rapid and potent germicides known.

AUTHOR'S SUMMARY.

FOWL PARALYSIS (NEUROLYMPHOMATOSIS GALLINARUM). ALWIN M. PAPPENHEIMER, LESLIE C. DUNN and BERNON CONE, J. Exper. Med. **49**:63, 1929.

Fowl paralysis is a disease entity, with characteristic clinical and pathologic features. The disease occurs in all parts of the United States, Holland, Austria and probably South America. The disease appears to be endemic in certain foci. Having once appeared, the disease tends to persist through successive years. It occurs with about equal frequency in both sexes; all common breeds may be affected. Symptoms appear between the third and eighteenth months. Typical clinical cases have not been observed outside of these limits. The conspicuous symptoms are asymmetrical, partial and progressive paralysis of the wings and both legs, and rarely of the muscles of the neck; occasionally, gray discoloration of the iris, with blindness. Nutrition is usually preserved. The duration is vari-



able; the outcome is usually fatal, but spontaneous recovery may rarely occur. The principal pathologic changes are found in the nervous system. In the peripheral nerves, the essential feature is an intense infiltration of lymphoid, plasma cells and large mononuclears. This is accompanied by a myelin degeneration in the more advanced lesions, but the cellular infiltrations appear to precede the degenerative changes. In the brain, cord and meninges, there are similar infiltrations predominantly perivascular. Infiltrations of the iris with lymphoid and plasma cells are found in the cases showing gross discoloration of the iris. Visceral lymphomas, originating usually in the ovary, are associated in a certain percentage of the cases. Evidence is presented in favor of the view that this association is not accidental, and that the lymphomas are a manifestation of the disease. Infiltrations of the spinal cord and brain, rarely of the peripheral nerves, are frequently present in birds showing no clinical symptoms. These are interpreted as mild cases of the same disease. No micro-organisms of etiologic significance have been demonstrated in the tissues or by cultural methods.

AUTHORS' SUMMARY.

TRANSMISSION EXPERIMENTS WITH FOWL PARALYSIS (NEUROLYMPHOMATOSIS GALLINARUM). ALWIN M. PAPPENHEIMER, LESLIE C. DUNN and S. M. SEIDLIN, J. Exper. Med. **49**:87, 1929.

Inoculation of suspensions of brain, cord, ganglions or nerves of chickens with neurolymphomatous lesions into newly hatched chicks is followed by the development of typical lesions in approximately 25 per cent of cases. In control chickens kept under laboratory conditions, the incidence of the disease is about 7 per cent. The disease does not become manifest until at least two months after inoculation; symptoms may not appear until after four months. The active agent is not destroyed by 50 per cent glycerol in nine days at icebox temperature.

AUTHORS' SUMMARY.

THE PATHOGENICITY OF THE AVIAN TUBERCLE BACILLUS. ELISE S. L'ESPERANCE, J. Immunol. **16**:27, 1929.

The results obtained in this series of experiments seem to indicate that it is possible to transform an animal relatively resistant to the avian tubercle bacillus into a more or less susceptible one, by previous treatment with a dead heterologous strain of tubercle bacilli.

AUTHOR'S SUMMARY.

EXPERIMENTAL INOCULATION OF CHICKENS WITH HODGKIN'S NODES. ELISE S. L'ESPERANCE, J. Immunol. **16**:37, 1929.

In chickens, a lesion with the histologic features of Hodgkin's granuloma, and comparable to avian tuberculosis, has been produced after the inoculation of emulsified Hodgkin's nodes. This may indicate that the etiologic agent in certain forms of Hodgkin's disease is pathogenic for birds, or that the avian tubercle bacilli are a factor in producing some of the lesions which are interpreted as Hodgkin's disease.

AUTHOR'S SUMMARY.

THE BROAD TAPEWORM IN AMERICA WITH SUGGESTIONS FOR ITS CONTROL. TEUNIS VERGEER, J. Infect. Dis. **44**:1, 1929.

The history of the broad tapeworm in America is briefly reviewed. The possibility of finding several other larval forms of the tapeworms of man in fishes is pointed out, and the necessity is stressed of rearing larval forms to adults for the purpose of identification. *Dibothriocephalus latum* is nearly world wide in its distribution. The life cycle, which is discussed, is not completely known. The plerocercoids are described and figured to aid in identification. It is demonstrated that fishes from all commercially important lakes in Canada are infested with the larval forms of *D. latum*. Prophylaxis is discussed.

AUTHOR'S SUMMARY.

EFFECT OF OXYGEN ON THE VIABILITY OF YOUNG CULTURES OF *CLOSTRIDIUM BOTULINUM*. GAIL M. DACK and ELIZABETH H. WILLISTON, J. Infect. Dis. **44**:27, 1929.

The viability of young cultures of *Clostridium botulinum* type A and type B exposed to oxygen for periods of from thirty seconds to one hour was greatly reduced. Only a small percentage of the organisms demonstrated by the hemacytometer count were viable.

The age of the culture is one factor determining the resistance of the cells to oxygen, the younger (twelve-hour) cultures being more sensitive than the older (forty-eight hour) ones. The type of menstruum in which the cells are suspended alters their resistance to oxygen. The number of cells surviving treatment with oxygen in salt solution is small, while if a phosphate buffered salt solution is used the viability is greater.

AUTHORS' SUMMARY.

INFECTIONS OF THE UPPER RESPIRATORY TRACT AND MIDDLE EAR. JOHN H. FISHER, J. Infect. Dis. **44**:33, 1929.

The pathogenicity of the organisms isolated from fifteen cases of infection of the middle ear in man was tested in rabbits by intranasal inoculations. The nasal passages of the rabbits were previously swabbed with a 50 per cent aqueous solution of phenol. Eleven of these rabbits died, and in each case acute purulent paranasal sinusitis and acute otitis media were found. From these lesions, in each instance, an organism similar to the type inoculated was recovered. Associated lesions, in some of the rabbits, were acute pleuritis and empyema, lobular pneumonia, abscesses of the lung, acute pericarditis and septicemia. From these lesions, in each case, organisms similar to those inoculated intranasally were recovered. The experiments were controlled by two groups of rabbits, one group receiving culture only, intranasally, the other receiving swabbing only. None of the rabbits of these two groups died. Some factor which lowers the resistance of the nasal mucosa is necessary for the infection of the upper respiratory tract and middle ear. In twelve untreated normal control rabbits there was no evidence of otitis media.

It is thought that the use of 50 per cent phenol as a means of reducing resistance of tissue may prove of value in the experimental infection of animals.

Fifty cases of acute infection of the middle ear in man were studied bacteriologically. *Streptococcus hemolyticus* was the exciting organism most frequently found, while *Staphylococcus* and *Pneumococcus* were next.

The evidence indicates that otitis media is not blood-borne, but develops by direct extension from an infection of the upper respiratory tract.

AUTHOR'S SUMMARY.

YEASTLIKE ORGANISMS OF HUMAN ORIGIN. MARGARET J. MCKINNEY, J. Infect. Dis. **44**:47, 1929.

Many of the yeastlike organisms occurring in routine hospital culture may be the etiologic factor of the pathologic condition under examination since eleven of twelve strains studied were virulent. One strain was avirulent for both guinea-pigs and rabbits, although it had been repeatedly isolated from the stools of a patient with chronic colitis.

Culturally, the yeastlike organisms were *Monilia*, producing mycelium and having no ascospores. They were only distantly related to the gram-positive budding organism from Fleischmann's yeast. Identification of the yeasts according to the table of biochemical characters given by Castellani was difficult, since they differed in one or more cultural reactions from those in his classification.

Immunization of animals with the organisms produced serums high in agglutinins and complement-fixation antibodies. The agglutination and complement fixation indicated a marked difference between Fleischmann's yeast and *Monilia* from human sources. One strain was more closely allied to Fleischmann's yeast in its

immunity reactions than to the pathogenic strains. With the exception of those of Fleischmann's yeast, the agglutinin and complement-fixation reactions showed only slight group or species specificity. In the small group of yeastlike strains studied, there was no clear correlation between the source, the cultural characteristics and the serologic reactions.

AUTHOR'S SUMMARY.

THE TRANSMISSION OF *BARTONELLA* IN ALBINO RATS. PAUL R. CANNON and PRESTON H. McCLELLAND, *J. Infect. Dis.* **44**:56, 1929.

The anemia following splenectomy in albino rats is due to a virus which is transmissible from rat to rat by inoculation of the parenchyma of the liver or by the blood. This infection is spread by contact of uninfected rats with infected ones. Lice from infected rats can convey the virus to uninfected rats. The infection is not readily spread by contact if the infected rats are completely freed from ectoparasites, particularly lice. The virus is presumably *Bartonella muris*. The mode of transmission indicates that the bartonella of Oroya fever may be transmitted similarly by the body louse (*Pediculus corporis*) or the bedbug (*Cimex lectularius*).

AUTHORS' SUMMARY.

"SMOOTH-ROUGH" VARIATION IN BACTERIA IN ITS RELATION TO BACTERIOPHAGE. F. M. BURNET, *J. Path. & Bact.* **32**:15, 1929.

There are characteristic differences in the behavior of the smooth and rough forms of *Salmonella* strains toward bacteriophage. Certain phage types are limited in their action to smooth forms, others attack only rough strains, while a third group may lyse either form. The type of resistant colony produced is related to these characteristics of the lysing phage. "Smooth" phages tend to give rough or partially rough resistants, "rough" phages with certain rough cultures provoke the appearance of true smooth forms, while those phages which lyse both forms impartially are more liable to show specifically resistant forms in the same phase as the parent strain. From cultures that are rough by all the usual criteria, it is possible by the use of suitable phages to derive true smooth forms showing all the characters of the type including active virulence. Some rough cultures could not be so converted to the smooth type, and the evidence, which is incomplete, suggests that the conversion can occur only so long as a trace of smooth antigen is retained in the antigenic make-up of the bacillus. The quantitative relations between the numbers of bacilli lysed and the numbers of the various types of resistant colonies strongly suggest that the appearance of a new phase (R or S) under the influence of phage is purely a selection phenomenon. Experiments are presented to disprove Bail's contention that phages which produce the same type of resistance with a single bacterial strain are necessarily qualitatively identical. A general discussion of the nature of bacterial resistance to phage is attempted from the standpoint that its most important factor is change in the bacterial constituent which also functions as the "heat-stable antigen."

AUTHOR'S SUMMARY.

BACTERIUM *MORGANI* FROM THE MAMMALS, BIRDS AND REPTILES. REGINALD LOVELL, *J. Path. & Bact.* **32**:79, 1929.

*B. morgani* was isolated from one bird, four monkeys and four reptiles, in circumstances which suggest this organism was etiologically related to the infection from which they died. No evidence was obtained that *B. morgani* is capable of producing a soluble exotoxin.

AUTHOR'S SUMMARY.

INTESTINAL BACILLI WITH SPECIAL REFERENCE TO SMOOTH AND ROUGH RACES. BRUCE P. WHITE, *J. Path. & Bact.* **32**:85, 1929.

The soluble specific substance may be extracted quantitatively from *Salmonella* and similar bacilli by hot dilute acid. Rough variants give an immediate reaction

with Millon's reagent; smooth races react only when the soluble specific substance has been removed. Under ordinary circumstances of test, smooth *Salmonella* and related bacilli and filtrates of broth cultures thereof are more toxic to laboratory rodents than are the corresponding rough bacilli and filtrates; the rough bacilli, however, possess a potential toxicity, disclosed by treatment with alcohol, approximating to that of the smooth forms. Mucoid growth in *Salmonella* has no relation to smoothness and is not analogous to capsule formation. The serologic reactions of rough variants appear to form a useful basis for a natural classification of intestinal bacilli.

AUTHOR'S SUMMARY.

GENERALIZED VACCINIA IN RABBITS WITH INTERNAL LESIONS. S. R. DOUGLAS, WILSON SMITH and L. R. W. PRICE, J. Path. & Bact. **32**:99, 1929.

A condition of experimental generalized vaccinia in rabbits is described which closely resembles human smallpox of the alastrim type. In this generalized disease almost every tissue of the body may be affected with the production of macroscopic lesions; no injury or irritation is necessary. The internal viscera most commonly affected are the lungs, liver, spleen, adrenal glands and the organs of reproduction. The kidneys are exceptional in that they have never shown generalized lesions. The mesodermic origin of an organ does not indicate a nonsusceptibility to vaccinia. A strain of testicular passage virus was obtained which was highly infective when introduced by intraperitoneal inoculation; it produced a vaccinal peritonitis and gave rise to pathologic lesions in organs hitherto thought to be nonsusceptible, for instance, in the uterus, bladder, peritoneum and muscle. Vaccinia virus may remain latent in the tissues of an immune animal for a long period (up to at least forty-one days) after infection. Virus was recovered from the blood of an animal six days after infection. Infectivity of the blood is irregular and appears to have no correlation with the time incidence of generalization. Vaccinal infection caused abortion in three pregnant rabbits in all of which there was particular localization of lesions in the uterus. Both placenta and fetus contained virus.

AUTHORS' SUMMARY.

THE POSSIBILITY OF AN ABACILLARY BUT VIRULENT STAGE IN THE LATENT PERIOD OF TUBERCULOSIS. H. DURAND, P. KOURITSKY and R. BENDA, Compt. rend. Soc. d. biol. **99**:30, 1928.

Durand and his co-workers observed a patient with clinically latent tuberculosis whose sputum after being thoroughly examined, was injected into guinea-pigs and caused the death of the animals within a period of from eighteen, twenty-five, twenty-eight to thirty days, respectively. The tuberculous lesions found in these animals were confined only to the lymph nodes and closely resembled those lesions found in guinea-pigs after inoculation with the tuberculous filtrable virus. There was no ulcer at the point of inoculation. Moreover, the filtrate from the same sputum led rapidly to an atypical tuberculosis in the guinea-pig. Later on, when the sputum showed the presence of tubercle bacilli and this was injected into the guinea-pig, the animal showed the usual type of tuberculosis. The authors think that in the antebacillary period tuberculous patients expectorate an "invisible" but active tuberculous virus.

B. M. FRIED.

TWO CASES OF HUMAN INFECTION WITH *BACILLUS ABORTUS*. S. LEGEZYSKY, Compt. rend. Soc. de biol. **99**:919, 1928.

The cases reported occurred in two veterinary physicians who came in close contact with sick cows. In one patient, the general symptoms were preceded by a furunculosis of the hand which assisted the abortion. The incubation period lasted from four to eight weeks. The outstanding clinical symptom was intermittent fever, which lasted six weeks in one patient; in the other there occurred two attacks at an interval of four weeks, each lasting fifteen days. The complement-fixation reaction and the agglutination test (1:1,600) were positive with the

abortus bacillus as well as with the Mediterranean fever micrococcus; the urine was negative for organisms, and the blood culture done after the fever subsided was sterile. The author affirms that Malta fever is entirely ignored in Poland, while the disease of the epizootic abortion is common. This fact plus the obvious exposure of the patients is definite proof that the veterinary physicians were infected with Bang's bacillus.

B. M. FRIED.

THE FILTRABILITY OF THE PFEIFFER BACILLUS. R. DUJARRIC DE LA RIVIERE, *Centralbl. f. Bakteriologie*. **106:30**, 1928.

The author injected cultures of the Pfeiffer bacillus intraperitoneally into guinea-pigs and observed granular forms in the peritoneal exudate at the end of an hour. This exudate was then filtered through Berkefeld and Chamberland L2 bougies at a pressure of from 20 to 30 mm. of mercury. Before and after the filtration, tests were made to determine the viability of the Pfeiffer bacilli. The filtrate was inoculated into blood and vitamin broth. In fourteen of sixty filtrations the results were positive, Pfeiffer's bacilli being found in the filtrate. The suggestion is made that these observations may serve to harmonize the views as to a filtrable virus and the Pfeiffer bacillus being the cause of influenza.

PAUL R. CANNON.

THE PFEIFFER BACILLUS IN POSTMORTEM MATERIAL WITH ESPECIAL REFERENCE TO EPIDEMIC-FREE PERIODS. KARL LIEBER, *Centralbl. f. Bakteriologie*. **106:190**, 1928.

Cultures of the trachea and bronchi of fresh cadavers were made in the effort to determine how frequently the Pfeiffer bacillus is present in nonepidemic as compared with epidemic periods. During the interval when grip was frequent, positive cultures for the Pfeiffer bacillus were frequently obtained; when warm weather appeared and grip disappeared, no positive cultures for the Pfeiffer bacillus were obtained in ninety-two consecutive necropsies. With the reappearance of cold weather and an increased incidence of grip, positive cultures were again secured, in one instance from the spinal fluid of a child with meningitis. The author concludes that the Pfeiffer bacillus regularly accompanies an influenza epidemic and in general, in epidemic-free periods, is not present.

PAUL R. CANNON.

"CENTRODERMOSES" WITH REFERENCE TO THE ETIOLOGY OF MEASLES. B. LIPSCHÜTZ, *Virchows Arch. f. path. Anat.* **267:233**, 1928.

Lipschütz classes measles with German measles, pityriasis rosea and lichen planus, as a "centrodermosis," meaning a skin disease characterized by pathologic changes in certain types of cells. Cytologic study of the eruption revealed characteristic pathologic types of "microcenters" in the histiocytes and epithelial cells in the region of the macules. Cells showing these abnormal bodies, centrocytes, were found constantly both in human material and in the skin of monkeys with experimentally produced measles. The author believes these changes to be due to the presence of an ultramicroscopic, filtrable virus in the skin.

B. R. LOVETT.

THE STABILITY OF VIRULENT STREPTOCOCCI. H. DOLD and H. R. MÜLLER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55:214**, 1928.

Streptococci of different virulence which had been kept for from eleven to thirteen months on artificial mediums were studied. A streptococcus strain of low virulence (type I) showed after seventy-two subcultures no change in its degree of virulence. An increase of virulence could not be accomplished by twelve animal passages. Two streptococcus strains of moderate virulence (type II) showed some decrease of virulence after they were subcultured for several months

on artificial mediums. The original degree of virulence, however, could be restored by from three to five animal passages. A highly virulent strain showed toward the end of the experimental period some weakening in virulence. Three animal passages were not able to restore completely the previous high degree of virulence. It is concluded that the strains studied showed a marked tendency to preserve their original degree of virulence.

W. C. HUEPER.

THE VARIABILITY OF PNEUMOCOCCI. F. NEUFELD and W. LEVINthal, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:324, 1928.

The degree of virulence of pneumococci can be preserved for years by growing them at 25 C. with subcultures every other day. Virulent pneumococci of type I in broth containing rabbit kidney kept at 37 C. are transformed after the third day into an avirulent form. The same change takes place in broth containing rabbit spleen while pneumococci grown in ordinary broth die after from two to three days. The addition of boiled kidney tissue keeps the pneumococci alive in an unchanged state for about six weeks. The experiments of Griffith are confirmed. An avirulent R-variety of type I injected into mice together with killed S-cocci changed into a typical virulent pneumococcus.

W. C. HUEPER.

ON THE BLOOD PICTURE AND HEMATOPOIETIC ORGANS IN EXPERIMENTAL RAT-BITE FEVER IN GUINEA-PIGS. Y. ISHIZU, Sc. Rep. Gov't Inst. Infect. Dis. **6**:267, 1927.

Experimental rat-bite fever in guinea-pigs produced a leukocytosis with a relative and absolute decrease in the lymphocytes and an increase in the number of pseudo-eosinophilic leukocytes and monocytes. The red blood cells and hemoglobin decreased together often with anisocytosis, poikilocytosis and basophilic stippling of the erythrocytes. The spleen was usually enlarged.

E. P. JORDAN.

### Immunology

ASTHMA IN CHILDREN. M. M. PESHKIN and A. H. FINEMAN, Am. J. Dis. Child. **37**:39, 1929.

Each of eighteen children with asthma, ranging in age from 7 months to 14 years, were tested by the direct and indirect methods with thirty-three protein extracts, both the scratch and intradermal technics being used. Dry powdered extracts were employed for the scratch tests, and routine fluid extracts for the intradermal. All of these children were under observation for two years. The indirect method of testing (scratch and intradermal technics) employed as a routine measure to determine etiologic sensitizations in children with allergy is unsatisfactory. Its employment as a substitute for the direct method of testing even in specially selected cases is not practical.

AUTHORS' SUMMARY.

B. WELCHII ANTITOXIN IN TOXEMIA OF INTESTINAL OBSTRUCTION. J. J. MORTON and S. J. STABINS, Arch. Surg. **17**:860, 1928.

Jejunal obstruction 10 inches (25 cm.) below the ligament is fatal in dogs in from three to ten days. Death is preceded by manifestations of a toxemia associated with changes in the chemistry of the blood, chiefly of the chlorides and non-protein partition. If the obstruction is relieved after the toxemia has developed, the condition is fatal. Some animals, however, recovered when *B. welchii* antitoxin was given intravenously. There is evidence that this antitoxin delays the onset of the toxemia. Other antitoxic serums did not have any influence on the outcome.

N. ENZER.

DISTRIBUTION OF AGGLUTININ IN THE LIVER AND THE LEG. JULES FREUND and CAROLINE E. WHITNEY, *J. Immunol.* **16**:109, 1929.

When rabbit serum containing agglutinins is injected into the vein of the ear in rabbits, agglutinins accumulate in the lymph of the liver rapidly, and in the lymph of the leg slowly. In immunizing animals passively, the titer of the lymph of the liver (obtained by cannulating a lymph vessel) may be as high as from 10 to 15 per cent of the titer of the serum within five minutes, and from 42 to 50 per cent within thirty minutes, after the injection of antibodies. The titer of the lymph of the leg is less than 10 per cent of the titer of the serum even six hours after passive immunization. When the accumulation of antibodies in the lymph is completed, the average of the titer of the lymph of the liver (75 per cent) is about twice as high as that of the lymph of leg (35 per cent). The rate of accumulation of antibodies in the passively immunized rabbit is rapid in the tissue of the liver and considerably slower in the muscles of the leg. The accumulation is completed in the liver within ten minutes; it continues for hours in the muscles of the leg. Perfusion of immunized rabbits *in vivo* or of the isolated liver reduces the agglutinin content both in the tissue and in the lymph of the liver. In the liver and in the muscle of the leg the parallelisms found between the tissues and their lymph, both as regards the rate of accumulation of agglutinins and the amount of agglutinins finally accumulated, are in harmony with the view that the agglutinins recoverable from tissues are the antibodies of the lymph, *i. e.*, of the intercellular tissue fluid.

AUTHORS' SUMMARY.

ON THE RACIAL DISTRIBUTION OF SOME AGGLUTINABLE STRUCTURES OF HUMAN BLOOD. K. LANDSTEINER and PHILIP LEVINE, *J. Immunol.* **16**:123, 1929.

Correlating all the known facts it is uncertain whether one will succeed in discovering immunologic qualities entirely specific for races analogous to the characteristics of the serologic species; one is rather led to the idea that the serologic make-up of races is determined by varying combinations of a number of characteristics.

AUTHORS' SUMMARY.

VITAL STAINING WITH TRYPAN BLUE IN SHOCK IN RABBITS AND GUINEA-PIGS. SUSAN GRIFFITH RAMSDALL, *J. Immunol.* **16**:133, 1929.

For the rabbit, the tissues of importance in the absorption of trypan blue from the circulation during shock were found to be the skin, the mucous membranes, the blood vessels and the liver. For the guinea-pig, the only tissue of importance was the skin. Since the appearance of the dye in the tissues is assumed to be only an indication of edema, one may conclude that such a change can play no significant part in acute shock in the guinea-pig, and that in the rabbit its effects are only indirect, producing the toxic rather than the acute syndrome usually manifested by this animal. This does not mean that the first effect of an antigen antibody reaction is not on the capillary endothelium. Possibly the ensuing permeability is the first step in a stimulation of the smooth musculature so great, in the guinea-pig, as to obscure the less spectacular edema, especially since the latter depends for its manifestation in a large measure both on the factor of time and on a special type of tissue that is rich in capillaries and connective tissue, which finds its highest development only in the skin.

AUTHOR'S SUMMARY.

THE RETICULO-ENDOTHELIAL SYSTEM AND ANTIBODY PRODUCTION. EDWARD F. ROBERTS, *J. Immunol.* **16**:137, 1929.

Evidence derived from a study of the effect of a reticulo-endothelial blockade in rabbits on the appearance of antibody in the circulating blood intimates a trend toward the inhibition of the rate and extent of the appearance of hemolysin, agglutinin and precipitin. The relative inefficiency of the method of so-called blockade and the factor of individual variation do not warrant the formulation

of definite conclusions from experiments of this kind. In addition to the predominant factor of individual variation among rabbits, the type of blocking agent, the dosage of the blocking agent, and the type of antigen are factors which account in large part for the diverse results reported in the literature.

## AUTHOR'S SUMMARY.

COMPLEMENT FIXATION REACTION WITH RABIES AND HERPES VIRUSES. FEI-FANG TANG and M. RUIZ CASTANEDA, J. Immunol. **16**:151, 1929.

Despite repeated attempts, the work of Takaki, Kraus and their co-workers could not be confirmed, and no evidence could be found that there are specific complement-fixing antibodies in the serum of rabbits immunized against the viruses of herpes and rabies.

## AUTHORS' SUMMARY.

IMMUNIZATION AND THE NITROGENOUS CONSTITUENTS OF THE BLOOD. M. F. GUYER and S. LEPKOVSKY, J. Immunol. **16**:175, 1929.

When a foreign protein such as that in the vaccine of *Bacillus typhosus* is injected into the blood stream of rabbits there results in general: a tendency toward diminution in the aminonitrogen content of the blood (except in moribund animals); a striking rise in nonprotein nitrogen; an increase in urea output, but scarcely enough to account for the full excess of nonprotein nitrogen; generally an obvious rise in the number of white blood cells; usually an elevation in temperature; lowering of the alkaline reserve; a lowering of the  $p_H$  which, in certain moribund animals, at least, along with the lowered alkaline reserve indicates an uncompensated acidosis; a rather prolonged inhibition of kidney secretion; a lowered specific gravity of the blood when water is administered, due to water retention; and in some cases a temporary acidosis of the body tissues.

That the results are due mainly to the foreign protein rather than to the ensuing fever is indicated by the fact that animals made febrile by infra-red radiation do not show the effects exhibited by the animals given injections of typhoid vaccine, although hemin has a tendency to produce the same changes in nonprotein nitrogen, urea nitrogen and the retention of urine. Apparently the aminonitrogen is deaminized in part, with reappearance of the nitrogen in urea. The lowered specific gravity of the blood when water is given by stomach tube, indicating dilution, is probably insufficient to account for all the water that had been administered prior to inoculation; hence, the inference is that some of it has been distributed through the body tissues. Tissue acidosis may be responsible for such distribution. The difficulty of getting blood from the ear veins in vaccine-treated animals and the marked diminution in flow of urine indicate a condition similar to that described by Brown and Loevenhart for animals receiving injections of hemin, when a pronounced fall in blood pressure and a marked dilation of the splanchnic vessels were accompanied by cessation of kidney excretion. Acute albuminuria produced by injection of uranium nitrate is not accompanied by the urinary effects which follow injections of protein; hence it is inferred that these effects are not the result of mere nephritis. From the data at hand, we have no way of determining whether or not the antibody itself is causing some of these changes.

## AUTHORS' SUMMARY.

QUANTITATIVE STUDIES ON THE ACTION OF COMPOUND HEMOLYSINS. RUDOLF GAHL, NORMAN DAVID and ALICE KELLEHER, J. Immunol. **16**:209, 1929.

New experimental material is presented in graphic form. The shape of the curves which are characteristic of the hemolytic reaction, their zones and the systems which they form were discussed in a qualitative way. One of the zones was proved to be due to the presence of amboceptor in the complement. It was proposed that another zone was due to the presence of complement in the amboceptor; this would imply that heat inactivation, at least as ordinarily conducted, does not destroy all the complement contained in the amboceptor before inactiva-



tion. A third zone was considered as representing the reaction between amboceptor and complement uncontaminated by side reactions. It was shown that this zone is utilized in the Wassermann test. It was also shown that the shape of the characteristics within this zone does not vary with the specimen of amboceptor and complement serum. Cross-section curves show the typical S-shape observed by Manwaring. This shape was found to be due to the varying resistance of the individual corpuscles towards lysis. The idea advanced in the second part of this paper, that the shape of the characteristic curves depends only on amboceptor and complement serum but not on the concentration and character of the blood corpuscles, was supported by experimental evidence.

AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES IN TUBERCULOSIS. S. A. PETROFF, ARNOLD BRANCH and F. B. JENNINGS, JR., *J. Immunol.* **16**:233, 1929.

From many years of study, it has become known that resistance to tuberculosis is manifested chiefly by a cellular reaction. Recent experiments have shown that the cellular reaction observed in animals sensitized with heat-killed tubercle bacilli does not differ from that seen in animals infected with living virulent organisms. Immunity produced by dead bacilli, therefore, is in no way likely to differ from that produced by living bacilli. From the studies of Bessau, Zinzzler, Ward and Jennings with guinea-pigs and from H. Langer's experiment on monkeys when he reduced the mortality in the Berlin Zoological Garden from 25 to 9 per cent after vaccination with heat-killed tubercle bacilli, and also from the observations given, it is thought that a vaccine of heat-killed tubercle can be put into practical use for the immunization of children. Good results may be anticipated. Heat-killed organisms as a vaccine are harmless for the reason that they do not propagate, while attenuated organisms entering the body may conceivably revert to their former pathogenicity.

AUTHORS' SUMMARY.

HETEROPHILE ANTIBODIES IN SERUM SICKNESS. I. DAVIDSOHN, *J. Immunol.* **16**:259, 1929.

The serums of twenty-one patients with horse serum sickness, whose blood was obtained during or at various intervals following the disease, were examined for agglutinins and hemolysins for sheep blood. Every one contained agglutinins for sheep blood, in titers varying from 1:4 to 1:64. Of 450 cases with no history of serum sickness, only 19 or 4.2 per cent showed agglutinins for sheep blood. All these 19 positive cases agglutinated only in the lowest dilution used (1:4). Four of the twenty-one cases showed a remarkable increase of antish sheep hemolysin, complete hemolysis occurring in the following dilutions: 1:192 (= 0.0026 cc.), 1:384 (= 0.0013 cc.), 1:768 (= 0.0006 cc.), 1:1536 (= 0.00032 cc.), while the highest titer found normally in a large series of control cases was 1:128 (= 0.004 cc.). Fresh sheep erythrocytes were somewhat less agglutinable than older ones; their hemolysis was not influenced by age. Only one serum lost its antish sheep agglutinins on standing. An immediate reaction in one patient following injection of horse serum is connected with the finding of agglutinins in a blood specimen obtained twenty hours following injection. The agglutinins were probably present before the injection of serum. In one of the cases of serum sickness and in one of the control cases the development of agglutinins following the injection of horse serum was observed by repeated titrations. Two patients developed agglutinins following the injection of horse serum, but no serum sickness. Three patients showed no agglutinins and no serum sickness following injection, while six patients found free from agglutinins before the injection of serum did not develop serum sickness. A patient with bovine serum sickness did not develop antish sheep hemolysins. The heterophile nature of the agglutinins and hemolysins found in the serum of patients with horse serum sickness was established by experiments on absorption.

AUTHOR'S SUMMARY.

DISTRIBUTION OF ANTIBODIES IN THE SERUM AND ORGANS OF RABBITS. JULES FREUND, J. Immunol. **16**:275, 1929.

The quantity of hemolysin recoverable from the spleen, uterus or skin of actively immunized rabbits varies in relation to the hemolysin titer of the serum. These organs contain about the same amount of hemolysin per gram of tissue. The ratio between the titer of the serum and the organ extracts varies between 10:0.6 and 10:1.25. With the method employed, precipitins cannot be recovered from the organs of rabbits immunized with horse serum, crystalline egg albumin or egg white.

AUTHOR'S SUMMARY.

ON THE HETEROPHILE (FORSSMAN'S) ANTIGEN IN THE PARATYPHOID-DYSENTERY GROUP. CLAUS W. JUNGBLUT and ALEXANDER T. ROSS, J. Immunol. **16**:369, 1929.

Immunization of rabbits with certain strains of *B. dysenteriae* Shiga or *B. paratyphosus* B was followed with great regularity by the appearance in the serum of hemolysins active for sheep and goat red corpuscles, but inactive for those of the human or rabbit. No formation of hemolysins was noted by immunizing guinea-pigs with the same cultures. Hemolytic Shiga and paratyphoid bacilli serums fixed complement specifically in the presence of true Forssman antigen. The heterophile antibodies in Shiga and paratyphoid bacillus serums were completely and specifically absorbed by contact with their homologous bacterial antigens as well as by absorption with true Forssman antigen. Intravenous injection of Shiga and paratyphoid bacillus serums into guinea-pigs was only occasionally followed by a characteristic systemic reaction due to primary antiserum toxicity. Intracutaneous injection into white guinea pigs and dogs induced frequently a well defined local, inflammatory reaction of the allergic type, particularly in the case of paratyphoid bacillus serums. Complement fixation between true Forssman antisera and Shiga or paratyphoid B bacilli as the respective antigens was not readily demonstrable. The reactions were faint and occurred irregularly. Absorption of true Forssman antisera by Shiga or paratyphoid B bacilli caused no definite loss of heterophile hemolysins in such serums. No evidence was found for the presence of heterophile antigen in strains of *B. paradyenteriae* (Flexner), *B. paratyphosus* A and B enteritidis (Gaertner).

AUTHORS' SUMMARY.

ANTIGENIC SUBSTANCES OF *CLAUSTRIDIUM BOTULINUM*. JEANNE LOMMEL and JANET B. GUNNISON, J. Immunol. **16**:403, 1929.

Substances have been obtained from *Claustidium botulinum* by extraction with 75 per cent alcohol, which contained little or no protein. They gave a positive Molisch reaction, indicating that carbohydrate was present. These substances gave strong complement fixation reactions with antibacterial immune serums. They were insoluble in salt solution and therefore failed to react in the precipitin test. They seemed to possess species specificity. The extracts had specificity neither for the serologic group nor for the toxicologic type. They apparently contained the non-specific factor responsible for the cross reactions observed among the serologic groups when intact organisms were used as antigens.

AUTHORS' SUMMARY.

LYSOZYME IN NORMAL TISSUES AND SECRETIONS. A. FLEMING, Lancet **1**:217, 1929.

Lysozyme is widely distributed throughout the body. It is found in most of the secretions and all the tissues of man, and is present in the tissues of other animals and in some vegetables. Although it may have some destructive effect on pathogenic bacteria, its extraordinary bacteriolytic effect is most easily shown on nonpathogenic bacteria, although even among these there are great differences in sensitiveness. Fleming succeeded in isolating a coccus which is remarkably sensitive to the action of lysozyme. Because it is easily dissolved he has called

this microbe *Micrococcus lysodeikticus*. When the concentration of lysozyme is great, as in tears or the white of egg, solution of this coccus is extremely rapid. The fact that lysozyme acts well on dead bacteria in an old culture is in striking contrast to the action of bacteriophage, which shows a lytic effect only on young, rapidly growing cultures. A great variety of tissues and secretions and excretions have been tested by Fleming with *M. lysodeikticus* and other organisms to see whether they contain this lytic principle. The principle was present in all the human tissues examined and in most of the secretions, except normal urine, sweat and cerebrospinal fluid. The concentration, however, varies greatly. Of all the tissues, cartilage had the strongest concentration, and an extract of cartilage corresponding to 1 part in 1,300 parts of physiologic solution of sodium chloride was capable of causing complete lysis of the test cocci in five minutes. On the other hand, the lytic action of brain tissue was weak. The great concentration of lysozyme in tears is striking. Lysozyme exists also in considerable concentration in leukocytes. The lysozyme content in the rabbit and the guinea-pig was much less than in man. The tissues of the dog stood midway between. The lysozyme concentration is greatest in the white of a hen's egg; a dilution as low as 1:60,000,000 has some lytic effect on the coccus. The yolk had no lytic action. The tissues of pike were found to contain much lysozyme, and its cartilage seemed to be quite as potent as that of man. The eggs of this fish were also found to be powerful. The tears of the rabbit, horse, sheep and turkey were all thirty or more times less potent than those of man in their action on *M. lysodeikticus*. Among the common garden vegetables tested, the turnip showed the greatest content in lysozyme, but even this was weak when compared with human tissues.

IMMUNITY IN RECURRENT FEVER. R. BRUYNOGHE and A. DUBOIS, Arch. internat. de méd. expér. 4:441, 1929.

Recurrent fever is peculiar in that the disease consists of several febrile attacks, each lasting a few days, the attacks themselves being separated by periods of apparent health. During the fever the patient's blood abounds in spirochetes which are easily demonstrable, while in the periods of apyrexia the blood is sterile. This curious phenomenon of an alternating invasion and disappearance of the germ from the blood is interpreted as follows: During the pyrexia antibodies appear in the blood which, in a few days, reach such a concentration as to destroy the bulk of the spirochetes. A few germs escape death, however, and develop a resistance to the lysis, thus being able to multiply and eventually to lead to a new access of fever. The disease then lasts until the formed lysins definitely overpower the spirochete.

Experiments have shown that the spirochetes of each subsequent attack differ from those of the preceding. Thus, for instance, when the serum from an animal cured from his first attack is inoculated with the spirochetes which caused this attack, the micro-organism is agglutinated and dissolved; but when the same serum is infected with a spirochete from a second attack, the germ is permitted to proliferate.

Numerous workers affirm that the changes which occur in the spirochetes during the fever and the apyrexia are so profound as to create virtually new races with entirely different biologic properties. They state, moreover, that the new characteristics are fixed forever. Bruynoghe and Dubois performed a series of elaborated experiments with spirochetes of various origin coming from Germany, France, Holland, and their own country, Belgium. They reached the conclusion that the spirochetes of different attacks vary only serologically. But when inoculated into new mice the germ loses its serologic identification, becoming the "spirochete of the first attack." They further affirm that the immunity in recurrent fever is specific; that is, the animal infected with a given strain resists reinfection with the same strain only. The immunity persists for a long period and cannot be induced by vaccination with dead germs. Many strains of spirochetes causing recurrent fever are arsenoresistant.

B. M. FRIED.

SPECIFIC CELL STIMULATION. G. BESSAU and C. DETERING, *Centralbl. f. Bakteriologie* **106**:11, 1928.

The authors discuss the relationship of immunity of cells to antibody production and present facts tending to indicate that the stimulation of cells may lead to the formation of specific products in these cells without any connection with antibodies in the blood. For instance, in certain infections an immunity can be present long after all antibodies have disappeared from the blood. They feel that the evidence indicates that the fundamental process of immunity is a "tuning" of the cell because of its experience with the antigen; secondarily, the secretion of the cell, the antibody, appears in the blood stream.

PAUL R. CANNON.

THE MECHANISM OF "PERCUTANEOUS IMMUNIZATION" AGAINST STAPHYLOCOCCUS INFECTIONS IN RABBITS. WERNER KOLLATH and HEINRICH HERFARTH, *Centralbl. f. Bakteriologie* **106**:120, 1928.

The influence of Besredka's "antivirus," ordinary bouillon, certain amino-acids and heat were tested on fresh intracutaneous and subcutaneous abscesses in rabbits. The virulence of the staphylococcus culture was increased by six intra-ocular passages. Various bouillons and peptone waters as well as such amino-acids as tryptophan, tyrosine, leucine, alanine and cystine restrained the inflammatory effect, whereas heat was without effect. Bouillon previously treated with ether, after preliminary acidification and alkalization, was distinctly more protective than ordinary bouillon. Therefore, the protective effects of different bouillons depend on the lipid content of the bouillons. This protective effect occurs only from the percutaneous injection, not from the intracutaneous. The effects were not manifested by such complete proteins as casein, depending apparently only on the peptone. The authors suggest that amino-acids in the peptone may cause the protective effect; these, however, have nothing to do with true immunity processes, but are strictly nonspecific.

PAUL R. CANNON.

## Tumors

MYOMA, SARCOMA AND CARCINOMA IN THE SAME UTERUS. Q. U. NEWELL, *Am. J. Obst. & Gynec.* **17**:191, 1929.

The neoplasms were found in the uterus of a negress, aged 57, who complained of pain in the lower abdomen and vaginal bleeding. The tumors were all in the uterine body. An adenocarcinoma was found to make up an edematous polypoid endometrial mass; there were multiple myomas, one of which showed sarcomatous changes. This case is the fifth reported case wherein all three types of tumor were found in one uterus and the twenty-first in which carcinomatous and sarcomatous changes were found.

A. J. KOBAC.

THE INCREASED MORTALITY RATE OF CANCER. H. E. EGGERS, *J. Cancer Research* **12**:9, 1928.

The relative frequency of cancer as seen at present in the clinic and at necropsy as compared with old observations is beyond contest. The question arises whether the noted increase is an actual, that is, absolute, increase in the occurrence of carcinoma or only an apparent one. To answer this complicated question, Eggers reasons as follows: Cancer is only one of a number of diseases that occur most constantly at a fairly advanced age; with it, in this respect, are associated what are usually termed the "degenerative" diseases, and if cancer is becoming more frequent largely because more people are reaching a suitable age, this group of diseases should show a proportionate increase. Eggers' careful investigation, embracing a period of twenty-five years (from 1900 to 1924 inclusive), is to the effect that the mortality incidence from cancer and that from degenerative dis-

eases, respectively, show a regular and even increase. He further states that the cancer death rate and the combined death rate from the other usual diseases of advanced age show an almost strictly proportionate rate of increase for the twenty-five year period. The increase, therefore, of cancer is in all probability more apparent than real.

B. M. FRIED.

OVARIAN SECRETION AND THE INCIDENCE OF TUMOR. WILLIAM S. MURRAY, *J. Cancer Research* **12:18**, 1928.

Murray's material consisted of mice "the genetic constitution of the individual members of which are as homogeneous as it is possible to make them." The technic of "homologizing" the animals consisted of the mating of brothers and sisters and also of back crossing of the young animals with their fathers and mothers. Working with such a stock of animals, he attempted to investigate: (1) the effect of nonbreeding on the incidence of tumor in this strain; (2) the effect of complete gonadectomy on the incidence of tumor and on the age at which tumor appears; (3) the inhibitory influence of the testicular hormone on the appearance of tumors, and (4) the effect of complete transplantation of the ovary on the production of mammary cancer in the male. From his experiments, it appears that virginity reduces the percentage of appearance of cancer and postpones the date of the appearance of cancer for about five months; complete gonadectomy lowers the incidence in a marked degree and also probably delays the age at which tumor appears later than in either the breeding animals or the virgin females. He believes that "something other" than the absence of the testicular secretions is necessary before males in this line will develop neoplasms of the mammary gland. His figures also show that the ovary successfully transplanted in a castrated male behaves in a manner that is similar, if not equivalent to that of the normal ovary in a virgin female.

B. M. FRIED.

HISTOLOGIC RESEMBLANCE OF THE ROUS CHICKEN SARCOMA NO. 1 TO HODGKIN'S GRANULOMA. F. A. MCJUNKIN, *J. Cancer Research* **12:47**, 1928.

McJunkin's ingenious experiments with Rous' sarcoma and with material from a malignant lymphoma led him to the conclusion that (1) both round and spindle-shape cells of chicken sarcoma no. 1 are actively phagocytic for carbon in suspension; (2) both round and spindle-shape cells of the chicken sarcoma react supravitaly with neutral red like blood monocytes; (3) the chicken sarcoma cells appear to be identical with monocytes, and (4) since the type cell of Hodgkin's granuloma corresponds closely with monocytic derivatives, the chicken sarcoma resembles Hodgkin's granuloma and is unlike the usual fibrosarcoma.

B. M. FRIED.

IMPLANTATION OF RAT CARCINOMA AND SARCOMA WITHIN BENIGN FIBROSARCOMA. JACOB HEIMAN, *J. Cancer Research* **12:73**, 1928.

Heiman inoculated rapidly growing carcinomas and sarcomas of rats into the centers of large spontaneous or transplanted fibromas or fibroadenomas of the breasts of other rats. This resulted in the growth of malignant tumors, but tumors with greatly reduced proliferative rates. In each case, the carcinoma continued to remain encysted in the center of the benign tumor, while the sarcoma seemed able to grow along the track of the needle, infiltrating the fibrous tissue and ultimately escaping into the tissues of the host. The benign tumor seemed to play a wholly neutral part, even though highly malignant cells were present in the center. This, according to Heiman, is further evidence against the hypothesis that an organism is responsible for the growth of malignant tumors, for one might expect that if such an organism were present it would stimulate the benign tumor to become malignant.

B. M. FRIED.

THE ETIOLOGY OF PRIMARY CARCINOMA OF THE LUNG. R. E. SMITH, J. Cancer Research **12**:134, 1928.

Smith investigated the specimens of primary carcinoma of the lung found at the Phipps Institute, University of Pennsylvania, with particular attention to the etiology of the tumor. He also carried on an experimental study of the same tumor in mice. For five months, respectively, two series of mice were exposed to fumes from coal tar and to fumes from the exhaust of a Ford engine, and a third series were painted with gasoline. Carcinoma of the lung did not occur in the series exposed to the fumes of coal tar; it occurred once in twenty-six (or 3.8 per cent) of the mice exposed to exhaust gas and once in twenty-nine (or 5.4 per cent) of the mice painted with gasoline. These proportions according to the author, are not greater than that of spontaneous occurrence of pulmonary cancer. The study of forty-eight cases of primary carcinoma of the lung in man did not reveal any definite etiologic factor. His observations are therefore against the suggestion that primary pulmonary cancer is caused by exposure to the fumes of coal tar or gasoline.

B. M. FRIED.

A NEW TRANSPLANTABLE RAT TUMOR. KANEMATSU SUGIURA, J. Cancer Research **12**:143, 1928.

The author describes a new type of transplantable rat sarcoma which on histologic examination resembles a small spindle cell myosarcoma. In his experiments with this tumor, he noted that there was a relationship between the growth of the tumor and the age of the host. Suckling and very young rats proved to be the most favorable soil for the continued growth of the sarcoma. In the young, regression of the tumor was present in 9.5 per cent only, whereas in the old it occurred in 87.5 per cent. However, the percentage of "takes" and their rate of growth were the same whether the hosts were young or old. He observed that rats immune to one type of tumor might or might not be immune to another kind. The transplantability of the sarcoma was completely destroyed by immersing the material in a Locke-Ringer solution or in a buffer mixture solution at pH 2, 3 or 4 for twenty-four hours at 3 C. The capacity of the sarcoma for growth was destroyed when the sarcoma was thus treated for thirty minutes at 45 C. Dehydration completely destroyed the viability of the fresh sarcoma. The tumor-producing substance of the rat sarcoma was not filtrable.

B. M. FRIED.

ON THE FILTRABLE AGENT OF MALIGNANT TUMORS. H. E. EGGERS, J. Cancer Research **12**:222, 1928.

Investigations by Burrows and others have shown that tissue of the rat embryo of fifteen and sixteen days' development, comminuted and inserted into adult rats of the same descent after being immersed in the filtrate from the Jensen rat sarcoma, took the form of a sarcomatous growth.

Eggers attempted to determine the possible presence of, and the character of the reaction to, tumor filtrates by tissues of postembryonic origin (using for injection a tumor filtrate of sarcoma no. 10 of the Institute of Cancer Research). He studied the effect on an induced growth of connective tissue in a relatively early stage of fibroblastic development. The results obtained are to the effect that in both rats and mice the injection of a freshly prepared filtrate of the rat sarcoma was followed by an increased proliferation of already developing connective tissue. This stimulation was of temporary duration and of limited extent, and in none of the animals observed did it take the form of malignant hyperplasia. The technic used by the author is given in detail.

B. M. FRIED.

BLOOD CHOLESTEROL IN CANCER. W. L. MATTICK and K. BUCHWALD, J. Cancer Research **12**:236, 1928.

In 85 per cent of patients with cancer somewhere in the body and likewise in cancerous mice, the cholesterol in the plasma was found higher than that in

the whole blood. But in noncancerous persons and in healthy mice, the plasma cholesterol was found lower than that in the whole blood. In view of the fact that similar studies were not performed on persons with diseases other than cancer, no definite conclusion can as yet be drawn from these observations.

B. M. FRIED.

THE GLYCOLYTIC ACTION OF SOME TUMORS AND THE EFFECT OF INSULIN. S. L. BAKER, F. DICKENS and E. J. GALLIMORE, *Brit. J. Exper. Path.* **10**:19, 1929.

A marked difference is found between the anaerobic metabolism of dextrose in normal tissues and that in malignant tumors, the latter producing from five to ten times as much lactic acid as the former. The addition of insulin or thyroxin has no demonstrable effect.

PEARL ZECK.

INTRA-EPITHELIOMATOUS HYPERGENESIS OF ELASTIC TISSUE. R. ARGAUD and J. DUCUING, *Ann. d'anat. path.* **6**:37, 1929.

In a cancer treated with the x-rays, the authors discovered an abundance of elastic tissue. A detailed investigation of the tumor led them to the conclusion that the epitheliomatous cell possesses the property of forming elastic tissue. It is possible, they say, that the elastic hyperplasia described in the vicinity of cancerous nodules of the breast is of epithelial origin.

B. M. FRIED.

A STUDY OF THE LIPOIDS OF RATS, CARRIERS OF ADENOCARCINOMA. ADA BOLAFFI, *Tumori* **3**:1, 1929.

In the bodies of rats, with the development of adenocarcinoma a remarkable impoverishment of phospholipins of the fraction soluble in ether and precipitated by acetone takes place. It is reduced to about one third of the amount found in normal rats. The tumors contain lipoids of this group in a proportion equal to or a little less than the average in the normal tissues. For this reason, the reduction of these lipoids in the tissues of the rats with tumors is apparently not due to a concentration of them in the tumors, but to a partial destruction of them in the bodies of the rats. The latter might be caused by an alteration of the lipid metabolism. In the tumors there is a certain concentration of lipoidal phosphorus, which may be due to the presence of unknown phosphatids that are rare or missing in the normal tissues. In other lipid fractions there is no appreciable difference.

W. OPHÜLS.

ON CERTAIN RESEMBLANCES BETWEEN THE TUMORS OF VEGETABLES AND THOSE OF ANIMALS. EUGENIO CENTANNI, *Tumori* **3**:17, 1929.

The tumors of animals and the tumors of vegetables resemble each other in their power of spontaneous development after they have been started by irritative agents. Extracts of the tumors of plants, do not stimulate the growth of the tumors of animals. This fact tends to show that the two differ considerably in their biologic activity.

W. OPHÜLS.

CARCINOMATOUS TRANSFORMATION OF ULCER OF THE STOMACH. E. KLEIN and F. DEMUTH, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:117, 1928.

The authors discuss first the clinical and histologic criteria on which may be based a decision as to the transformation of ulcer of the stomach into carcinoma. How differently these criteria may be interpreted by different observers is attested by the fact that Konejzky reported carcinomatous transformation as occurring in 3 per cent of ulcers, Hauser in 6 per cent of ulcers and in 7 per cent of scars of ulcers, whereas Wilson and MacCarty reported it as occurring in 71 per cent.

The work of the authors was concerned, not with the study of a large series of gastric ulcers to determine how many might show carcinomatous changes, but with the careful study of a small series of ulcers some of which showed carcinoma and some not, with the aim of determining whether any changes other than those easily recognized as carcinomatous might be considered characteristic of carcinoma. Moszkowitz had described groups of deeply staining epithelial cells as histologically pathognomonic of carcinoma. Klein and Demuth do not believe that the histologic diagnosis of carcinoma can be based on such cells nor on single cells, no matter how atypical or heterotopic. They lay greatest stress on the relatively greater formation of scar tissue in the submucosa at the margin or base of the ulcer when the latter becomes carcinomatous than when it remains benign.

O. T. SCHULTZ.

CHROMAFFIN TUMOR OF ZUCKERKANDL'S ORGAN. ERNA HANDSCHIN, Beitr. z. path. Anat. u. z. allg. Path. **79**:728, 1928.

A tumor of Zuckerkandl's organ, which the author had the opportunity to study, led to a histologic investigation of this paraganglionic tissue to determine the time of disappearance of its chromaffin tissue and whether it might persist late enough in life to account for tumors encountered in adult life. Regression of the chromaffin tissue begins at the end of the first year of life and continues fairly actively until puberty. Some chromaffin cells, however, were found in a person aged 26. No ganglion cells were seen at any age period. The tumor studied occurred in a man aged 45 and was a chance observation at necropsy, the patient having died after resection of the stomach for carcinoma. Blood pressure had been normal and there had been no clinical symptoms that might be ascribed to the tumor. The latter measured 3.5 cm. in its greatest dimension. Its cut surface was pale and somewhat translucent. Microscopically, it was moderately cellular, but did not give the impression of active growth. The tissue did not give the chromaffin reaction, but an extract made from a portion of the fresh tissue had the characteristic effect of epinephrine on the pupil of the excised eye of a frog. The tumor is believed to have arisen from persisting chromaffin cells. Because chromaffin tissue occurs in what have been called glands of internal secretion, the author makes the unfortunate suggestion that the tumor described by her is an adenoma.

EPITHELIOMA (SQUAMOUS CELL CARCINOMA) OF THYROID. M. KARTAGENER, Beitr. z. path. Anat. u. z. allg. Path. **79**:843, 1928.

The author describes a squamous cell carcinoma of the left lobe of the thyroid of a man, aged 64. There was no hornification. The esophagus and trachea were invaded, but the author does not think that the tumor originated in either of these structures, but in the thyroid itself. The reason for the reporting of the tumor lies in the fact that it contained also perithelioma-like areas. These consisted of large cylindric cells the bases of which lay directly on the endothelium of a capillary network. The cells were epithelial in type. The author considers this element in the tumor not a true perithelioma but a carcinoma derived from the glandular epithelium of the thyroid. He discusses the possible origin of the squamous cell portion by metaplasia or from misplaced squamous epithelium, but comes to no decision.

O. T. SCHULTZ.

CHLOROMYELOSIS WITH AN UNUSUAL EOSINOPHILIA. G. SEEMANN and A. SAJZEWA, Folia Haemet. **37**:258, 1928.

The patient, a man aged 42, showed a temperature of 38 C., a slight swelling of the cervical lymph nodes and some recent loss of weight. He complained of weakness and generalized pain. The blood picture, except for an eosinophil count of 49 per cent, was negative. The necropsy revealed chloromas that were confined to the periosteum. The high eosinophil count noted for smears was also found for the tissues. The authors designate the disease as chloromyelosis, including it in the group of leukemias.

B. M. FRIED.



OVARIAN ADENOMA. O. HEESCH, *Virchows Arch. f. path. Anat.* **268**:280, 1928.

The author concludes that adenoma tubulare ovarii of Pick is identical with the tubular adenoma of the atrophic testicle; also that other forms of tubular ovarian adenoma may occur which in their morphologic details closely resemble that of the testicle, but the true identity of which is not entirely clear.

V. C. JACOBSEN.

### Medicolegal Pathology

OCCUPATIONAL POISONING IN MANUFACTURE OF LUMINOUS WATCH DIALS.  
HARRISON S. MARTLAND, *J. A. M. A.* **92**:466, 1929.

Five of fifteen deaths known to have occurred among 800 girls employed in painting watch dials with luminous paints were proved to be due to radium poisoning. The exact number who have died of or who have been harmed by this disease is unknown. Various factors are involved in the production of this occupational poisoning other than the pointing of the paint brushes with the lips. The luminescence was produced by scintillation. Radon, radium, mesothorium or radiothorium was mixed with zinc sulphide and salts of rare earths; from 0.7 to 4 mg. of radium element was present in 100 Gm. of zinc sulphide; from 15 to 215 micrograms of radioactive substance was the theoretical amount ingested each week. From 14 to 48.282 micrograms was found in entire skeletons. The so-called lethal dose, estimated as radium element, ranges from 10 to 180 micrograms.

Necrosis of the jaw, leukopenic anemia, severe buccal lesions and terminal sepsis were present in the fatal cases. Symptoms were first noted from one to seven years after the patients ceased working as dial painters. Chronic radiation osteitis and subsequent bone lesions are present in patients still living. During life the diagnosis may be made by the demonstration of either emanations by means of an electrometer or alpha particles (from expired air), by scintillation methods. After death the diagnosis may be based on the radioactivity as determined in the bones by photography and in the soft tissues by the alpha or gamma electroscope.

The author interprets the disease as follows: After ingestion of the radioactive substance it is deposited in the form of an insoluble sulphate in the phagocytic cells of the sinusoids of the reticulo-endothelial system, especially in the bones, liver and spleen. In the bones the juxtaposition of the blood forming centers and the affected cells of the sinusoids, whence the destructive alpha rays emanate, produces the characteristic blood changes.

The preponderance of mesothorium is of toxicologic importance; it can produce in exposed persons aplastic anemia, myelogenous or lymphatic leukemia, sarcoma, sterility, radiation osteitis, necrosis of the bone and hemorrhagic diathesis, and endocarditis, sepsis or septic bronchopneumonia may be superimposed.

The hemorrhagic diathesis may be produced by a diminution of the blood platelets, either by direct effect of the alpha particles on the megakaryocytes or secondary to the sepsis. The blood picture shows a color index above unity; anisocytosis with macrocytes and megaloblasts; icterus index normal or below; negative van den Bergh reactions. "At autopsy there was no pronounced increase in hemosiderin deposits in the liver, spleen and kidneys, such as is seen in addisonian anemia." The bone-marrow of the femurs was dark red (hyperplastic) in all cases examined.

Radium-mesothorium necrosis is now one of only ten occupational diseases which come under the compensation laws in New Jersey. In 1926 the families of two girls dying from radium-mesothorium necrosis received compensation. In the case of the five girls said to be suffering with the disease, an uninvolved judge arranged for a settlement out of court. No legal responsibility was assumed by the company.

E. L. BENJAMIN

RUPTURE OF ESOPHAGUS BY INDIRECT VIOLENCE. J. R. MURDOCK, *Lancet* **2**: 1292, 1928.

A boy, aged 6 years, was run over by a motorcycle and died a few hours later. There were fractures of the left humerus and of the left side of the base of the skull; and also a longitudinal tear,  $1\frac{1}{4}$  inches long, in the esophagus  $\frac{3}{4}$  inch above the diaphragm which was torn slightly at the esophageal opening.

ASTONISHING REVELATIONS AT POSTMORTEM EXAMINATIONS. R. KOCKEL, *Arch. f. Kriminol.* **83**:242, 1928.

An extensive comminution of the cranial bones and injuries of the brain were found in the body of a man lying dead so far from where an explosion occurred that it was thought he had died from heart disease. A similar mistake was made in giving heart disease as the cause for death of a man found on a railroad track and a woman found on the street. Postmortem examination disclosed extensive crushing injuries in each body. Two other deaths supposed to have occurred from heart disease turned out to be due to bolus asphyxias.

Exhumation and examination of the body of a man pensioned for many years for an alleged heart disease following injury of the chest, not only failed to reveal any justification for the pension, but demonstrated that death was caused by a phlegmonous inflammation of the face. The attending physician had attributed death to the injury years before, and on that basis it was planned to have the pension continue to the family. Three deaths from electrocution are reported, but the exact manner of death was not learned until careful inquiry was made of the circumstances, an absence of disease and injury in the bodies established, and further examination had revealed small external wounds made by the current. Carbon monoxide was suspected as the cause for one of these deaths, and it was said that a second of the three persons electrocuted had suffered from heart disease for a long time. The attending physician had certified that as the cause of death.

A young married couple fought, and the husband killed his wife with a hatchet. He then set fire to the body with petroleum in the kitchen and went away. He confessed when told of the absence of soot in the lungs and of carbon monoxide in the blood, of the postmortem character of the burns and that a microscopic examination had demonstrated feathers in the burned clothing. The feathers were from a pillow that had become blood-stained. In the body of a man pensioned since the war for pulmonary tuberculosis and some nervous disease, these were found absent; death was caused by influenza. Two other deaths from hydrofluoric acid are reported; both were criminal poisonings of women by a man which were unexpectedly encountered. Death supposedly due to a street accident turned out to be from pernicious anemia and spontaneous hemorrhages; ruptured liver with huge hemoperitoneum was found in another body when it was supposed that injuries of the head had caused death.

It is difficult to accept the conclusions given by Kockel for the remaining one of the sixteen deaths, each with surprising revelations, with which his article is concerned. It has to do with a street fight and stab wounds of one of the combatants, the removal of 1 liter of blood from his chest two days after the fight and death with a fever four days after the thoracentesis. At the postmortem examination it was decided that none of the stab wounds, some of which were in the thorax on the side tapped, were mortal and that the fluid removed during life was in reality the bloody exudate of a pleuritis present at the time of the fight. Pleurisy was given as the cause of death. This account should include a description of what was done, if anything, to ascertain their depth and also whether any healing had taken place in any of the wounds of the chest during the six days the man lived.

E. R. LE COUNT.

# Society Transactions

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## PHILADELPHIA PATHOLOGICAL SOCIETY

*Regular Meeting, Feb. 14, 1929*

J. HAROLD AUSTIN, M.D., *President*

A CASE OF SEPTICEMIA IN MAN DUE TO BACILLUS SUIPESTHER. JOHN T. BAUER and MARGARET MCCLINTOCK (by invitation).

Organisms of the paratyphoid group other than *B. paratyphosus* A and B can give rise to febrile conditions in man, simulating typhoid fever. The following case illustrates the importance of further studies in instances in which the Widal test is negative for *B. typhosus* and *B. paratyphosus* A and B, and organisms isolated from the patient fail to react with the usual diagnostic typhoid and paratyphoid serums.

An Italian stone mason, aged 46, was admitted to the medical service of Dr. Norris at the Pennsylvania Hospital in August, 1927, with symptoms of headache, weakness and fever. Although no rose spots were seen, the clinical manifestations of a temperature of 103.8 F., a pulse rate of 92 beats per minute, a palpable spleen and liver and a leukopenia of 6,000 cells strongly suggested typhoid fever. The condition failed to improve, and death occurred on the twenty-first day of the disease. Permission for necropsy was not obtained. The source of infection was unknown, but the drinking water was suspected.

Three blood cultures were taken, and all yielded organisms which culturally proved to belong to the hog-cholera group. Two Widal tests were negative for *B. typhosus* and *B. paratyphosus* A and B, yet they showed strong agglutination in a dilution of 1:10,000 for *B. suipestifer* and the organisms isolated from the blood of the patient. By means of reciprocal agglutinin absorption tests, the close relationship of this organism to *B. suipestifer* was confirmed.

This article will be published in full in the *Journal of Infectious Diseases*.

SIMPLIFIED METHOD OF INJECTING THE CORONARY CIRCULATION. JOHN EIMAN and ETHEL L. RAHE.

Numerous methods have been employed for the demonstration and study of the circulation of the heart. They include dissection and injection with metals of low melting point and other substances, followed by corrosion. Later stereoscopic roentgenograms and clearing methods were introduced. Some of these methods were employed for special problems, such as the study of anastomoses, variations in the branches and distribution of the branches of the main vessels. Dr. Merritt B. Whitten (*Arch. Int. Med.* **42**:846 [Dec.] 1928), published an exhaustive review of the literature on methods of study of the circulation of the heart.

The method we are describing is not new. In 1896, Hermann Braus was apparently the first to inject the coronary arteries with a metal and to study stereoscopic roentgenograms (*Anat. Anz.* **11**:625, 1896). Oberhelman and LeCount (*J. A. M. A.* **82**:1321 [April 26] 1924), employed the foregoing method, using mercury.

Our technic of injection is as follows: Hearts are removed without injuring the musculature and with fairly long portions of the large vessels remaining. Clots are removed from cavities of the heart, and the blood is washed out with running water. The heart is placed on an aluminum tray covered with a towel. The aorta is slit on the anterior surface almost down to its origin. Cannulas are inserted into the coronary arteries. A heavy ligature is passed around each cor-

onary artery, as close to its origin as possible, by means of an aneurysm needle. Ligatures are tied firmly but not too tightly, and the cannulas are withdrawn until their flanges rest against the ligature.

Purse-string sutures are placed loosely around the orifice of the inferior vena cava and the largest of the pulmonary veins entering the left auricle. In order to distend slightly the cavities of the heart, two pieces of Esmarck rubber tubing should be introduced into them, which measure approximately 20 by 4 cm., one end of which has been made airtight and the other end attached to rubber pressure tubing. The tubing from the Esmarck drains is connected to a metal "Y" to the single end of which is attached by means of rubber tubing, an ordinary blood pressure bulb. One should tighten the purse-string ligatures in order to keep the Esmarck tubing in place, and should inflate the same and clamp the rubber tubing. Care must be taken not to overdistend the cavities, as this would interfere with the injection of the vessels. Mercury is placed in a separatory funnel which is attached to an upright stand by means of a clamp. Rubber tubing is attached to the funnel, and in its free end an adapter is fastened securely, which fits the cannula. The mercury level is adjusted to about 150 cm. above the midplane of the heart, all the air is expelled from the tubing and the tubing is clamped securely. The stop-cocks of both cannulas should be open. The adapter should be inserted into the cannula opening into the left coronary artery. The mercury is slowly released and permitted to flow into the arteries. If there is any escape of mercury from the smaller vessels, these should be clamped and tied off. Within from forty-five to one hundred and twenty seconds, mercury appears at the mouth of the cannula inserted into the right coronary artery. The stop-cock of the cannula in the right coronary artery should be turned off, and four or five seconds later that of the left. The tubing from the reservoir of mercury should be clamped and disconnected. The tip of the heart is elevated by means of the towel on which it is lying so as to remove any loose mercury that has escaped into the chambers of the heart. Stereoscopic roentgenograms are then made of the heart.

The cavities of the heart should be opened as soon as possible, and examined and described. Sections are taken for microscopic study.

Sometimes there is considerable escape of mercury through the thebesian veins. We have not succeeded in forcing mercury over into the veins of the heart even with a pressure up to 500 mm.

By this method it is impossible to inject the capillaries, precapillaries or even slightly larger vessels. It gives, however, excellent pictures of the gross circulation of the heart and enables one to visualize the coronary circulation in its entirety. This method supplies data that enable one to interpret more accurately gross and microscopic observations and to correlate them with the clinical picture of the case. Oberhelman and LeCount, on injecting twenty-six hearts, found that in nine both coronaries could not be injected by forcing mercury into the orifice of one coronary. In sixty adult hearts into which injections were made, we experienced such difficulty in only two cases, one case of occlusion of the orifice of the right coronary, the other of embolism in the left coronary. In cases of thrombosis and embolism, if the occlusion of the coronary occurs about 1 cm. or more from the orifice, the portion of the coronary proximal to the occlusion is filled through anastomosing branches. In cases of gradual occlusion of the main trunks of the coronary arteries or their larger branches, compensatory enlargement of anastomosing branches can be demonstrated in some instances.

Spalteholz (*Die Arterien der Herzwand*, 1924), Gross (*Blood Supply of the Heart*, 1921) and others have shown that near the surface of the heart of the new-born infant anastomosing arterioles exist between the right and the left coronaries. They were not able to demonstrate any anastomosis in the interventricular septum. When injections were made into hearts of new-born infants and children of  $2\frac{1}{2}$  years, we could not force mercury from the left coronary into the branches of the right. In a child, aged 5 years, both coronaries were completely injected through the orifice of the left. This suggests that anastomoses between larger vessels do not exist at birth, but that they develop some time between the ages of  $2\frac{1}{2}$  and

5 years. There is a rather strikingly different appearance between the branches and the distribution of the coronaries of children and young adults, on the one hand, and older adults on the other. In children the branches are fewer, coarser and of rather uneven distribution. In young adults, the anastomoses between the left and the right coronaries are maintained through one, two or three larger branches. We have been designating the latter type of arterial tree as juvenile. Occasionally, we have seen the juvenile type of anastomosis in older adults. It is rather difficult to interpret what this means. Would it not be possible that in cases in which the main anastomoses are maintained through one or two larger branches, the patient would die rather suddenly if one of those branches should become occluded? It is more than probable that in cases of thrombosis or embolism the question of patients surviving or dying depends on the efficiency of anastomoses between the right and the left coronaries. Nusbaum (*Arch. f. mikr. Anat.* 80:450, 1912) and Gross have reached the conclusion that capillary and precapillary anastomoses were inadequate to maintain sufficient collateral circulation in emergencies but may become adequate with gradual occlusion.

Changes in the lumina of the larger vessels due to arteriosclerosis are readily demonstrated. The outline of the vessels is irregular; disproportionate narrowing at bifurcations or origins of branches are seen. Sometimes calcareous infiltration of the walls is apparent. Although the changes are most striking in the larger vessels, damage or changes in the myocardium are seen around the capillaries and arterioles. In cases of sclerosis of the coronaries, diminution in the numbers of capillaries, compression and obliteration are seen. There are retrograde changes in the muscle cells around these capillaries and replacement of degenerated muscle cells by connective tissue. As the sclerosis of the larger vessels becomes more marked, the degeneration of muscle and the proliferation of connective tissues likewise become more extensive.

If possible, the injection of the arteries should be done in all cases that come to autopsy, but particularly in cases with a history of heart disease. The information gained by this simple method is of great value and offers many possibilities for the study of the coronary circulation in general.

It enables one to determine: (1) the location and extent of thrombosis; (2) the location of the emboli; (3) the degree and extent of sclerosis of the arteries, and (4) the rôle of the coronary vessels in their relation to myosclerosis.

#### A THEORETICAL CONSIDERATION OF THE INTERRELATION OF CERTAIN IMMUNE REACTIONS CONCERNED IN THE PRODUCTION OF CHRONIC DISEASE. James C. SMALL.

The hypothesis was suggested that certain of the manifestations of chronic disease depend largely on an abnormal state of a person, rather than on any unusual pathogenicity of the bacteria concerned in its etiology. The hypersensitive or allergic state of a person to a bacterial antigen was discussed and an attempt to explain the manner in which such a state may act continuously in producing chronic disease was presented in the light of the knowledge of such states induced in experimental animals.

The guinea-pig into which injections of horse serum are made was chosen as an example. From the time the animal receives a single injection onward, it can no longer be considered in a normal state. At the end of a period of days, it becomes so abnormal that a hundred-thousandth or a millionth part of the original injection of horse serum will produce rapid death. There has been no change in the inherent nature of the horse serum by virtue of which it can be regarded as any different chemically from the relatively inert substance it was for the animal primarily. The changed conditions, therefore, must be sought in the animal, which has become hypersensitive to the horse serum. Under proper conditions of the experiment, this hypersensitive condition may be maintained for indefinite periods. As long as the animal is in this condition, injections of small amounts of horse serum are likely to produce a fatal result, and injections of extremely minute amounts will produce tissue damage without an immediate fatal result.

One has, therefore, the conditions necessary for producing pathologic lesions over an extended period by the exhibition in minute amounts of a substance not primarily harmful to the animal. In this conception, then, there is a logical basis for the continued low-grade activity of chronic lesions in man. An insignificant focus of infection with streptococci, for example, may conceivably hypersensitize a person to some of the products of the bacteria. The constant supply of this antigenic substance from the focus continues to furnish the irritant responsible for widespread chronic degenerative lesions. This conception eliminates the necessity of attributing a primary highly pathogenic property to the streptococcus, since it, as the horse serum, may have in its primary contact with the animal organism feeble irritating properties.

This conception raises a fundamental question in treatment. After diligent search for, and careful elimination of, the foci of low-grade infection which presumably chiefly maintain the allergic state, is the problem in specific therapy that of immunizing or that of desensitizing the patient? There is suggestive evidence from the experimental standpoint that the hypersensitive state may be an indication of the beginning of the immunity. If the immune state can be raised to such a height that hypersensitive phenomena are no longer present, this procedure obviously promises the more permanent benefit. When this is not possible, the method of desensitization is available and offers the advantage of more prompt responses which, however, may not be permanent unless the principal sensitizing foci of infection have been eliminated.

#### SPONTANEOUS TUBERCULOSIS IN SNAKES. JOSEPH D. ARONSON.

Four garter snakes (*Thamnophis sirtalis*), which died at the Philadelphia Zoological Garden, showed the following lesions at necropsy: The livers of all of them were studded throughout with miliary tubercles. In one, a cavity containing mucopurulent material was found in the connective tissue above the upper pole of the liver. The right lung of three of the snakes contained areas of consolidation, and the peritracheal lymph nodes were swollen. In two specimens the spleen was swollen, soft and a uniform gray.

Histologically, the lesions from the various organs were found to be similar and to consist of a diffuse-staining center surrounded by layers of large cells with clear vesicular nuclei. A layer of dense connective tissue separated the lesions from the adjacent tissue, and numerous deeply staining cells and eosinophils were found throughout the section. The pulmonary alveoli contained numerous desquamated cells and numerous eosinophilic cells. No calcification or giant cells were noted. A small number of extracellular, beaded, acid-fast bacilli, as well as a large number of nonacid-fast bacilli having the same morphology, were scattered throughout the tubercle.

In the smears prepared from the various organs, from the cavity above the liver and from the cultures, an acid-fast pleomorphic bacillus was noted. Numerous beaded and barred forms were also found.

The bacilli stain readily with carbolfuschin and retain the stain when exposed to 25 per cent sulphuric acid for ten minutes, but many of them are decolorized by a three-minute exposure to hydrochloric acid, 5 per cent nitric acid or 10 per cent sodium sulphite. When exposed for three minutes or longer to 95 per cent ethyl alcohol, the organism is completely decolorized; it is gram-positive.

The bacillus grows readily at 25 C. on Dorsett's medium, Petroff's medium and on glycerin-agar. The colonies are elevated, moist and pink, later becoming salmon color.

The cultures were found to be pathogenic for goldfish, frogs, snakes, chameleons and lizards, but nonpathogenic for rabbits, guinea-pigs and chickens.

By means of the agglutination test and of absorption experiments, it was found that cultures isolated from the various snakes were antigenically the same and that they differed from *M. marinum*, *M. chelonae*, *M. ranarum* and from the acid-fast bacillus isolated by L. Rabinowitch-Kempner from boa-constrictors.

The organism isolated from these snakes is considered a new species, for which the name *Mycobacterium thamnophaeos* is proposed.

RATE OF ABSORPTION OF HORSE SERUM AFTER INJECTION AND ITS RELATIONSHIP TO SERUM DESSENSITIZATION AND SERUM THERAPY. LOUIS TUFT.

By means of the precipitation test, with the use of antihorse immune rabbit serum to provide the antibodies, it was possible to detect the presence of horse serum in the circulation after subcutaneous or intramuscular injection, and in this way to determine that after either method of injection in the three patients studied horse serum is slowly absorbed from the tissues, the major portion being absorbed in from fifteen to twenty-four hours. The amount of horse serum in the circulation then remains practically stationary for three or four days; then it slowly decreases in amount until at the end of seventeen days only a trace can be detected. In one case, study of the urine for horse serum after injection proved negative; evidently, this serum is not filtered out as such by the urine. The slow rate of absorption of horse serum offers a possible explanation of the failure of the usual methods of desensitization to protect against fatalities in the reported cases. It is therefore suggested that the methods of desensitization now in use be modified so as to allow a period of at least from fifteen to twenty-four hours, during which time enough of the horse serum may be absorbed to bring about desensitization. The method suggested consists of an injection of 0.1 cc. intramuscularly, followed in one-half hour by 0.3 cc., after an hour by 0.5 and after two hours by 1 cc. If no reaction occurs after a subsequent lapse of two hours, then the remainder of the serum can be given in divided doses every three hours over a period of twenty-four hours. If intravenous administration is paramount, it should be preceded by intramuscular injections over a preceding period of twenty-four hours and then intravenous injections of increasing doses every hour, any sign of untoward reaction being watched for carefully.

Preceding any form of serum therapy and irrespective of the method, a skin test with horse serum should be done. If the reaction is negative, the serum may be given with safety. If positive, it may indicate the presence of either a natural form of hypersensitiveness or an acquired or induced form. The studies and experiences mentioned suggest that serum desensitization in the human being should be limited only to patients with an acquired or induced form of hypersensitiveness to horse serum and should not be attempted in the natural or atopic form, in which it is not only ineffective but may be dangerous. Too much reliance should not be placed on any method of desensitization in the human being, the efficacy being at best doubtful. Finally, a slow absorption rate for horse serum suggests a similar state for immune antibodies; hence, intravenous administration is always preferable for a rapid clinical effect, unless contraindications exist.

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Meeting, March 11, 1929*

ESMOND R. LONG,

*President, in the Chair*

ON THE OCCURRENCE OF TRUE MIXED CARCINOMATOUS AND SARCOMATOUS TUMORS (SARCOCARCINOMA) WITH REPORT OF A MIXED CARCINO-CHONDROSARCOMA OF THE THYROID OF A DOG. ROBERT MASON AND H. GIDEON WELLS.

The infrequency with which malignant tumors present histologic features indicating that they are composed of both carcinomatous and sarcomatous elements is so striking that at times the existence of true mixed sarcoma and carcinoma has been questioned. As bearing evidence on the disputed question as to the genuineness of mixed sarcomas there was reported a case of a large mixed tumor arising in the thyroid of a dog. The tumor consisted of a mixture of adenocarcinoma with osteoid sarcoma. There were many metastases in the lungs, some

consisting solely of carcinoma, some solely of osteoid sarcoma and some presenting a mixture of both elements. Carcinoma cells could scarcely simulate such cartilaginous and osteoid structures, and hence there can be little room for doubting that these are truly sarcomatous portions of a mixed tumor. The occurrence of metastases showing only carcinomatous elements, and metastases of pure sarcomatous character, supports further the assumption that in the primary tumor there were both carcinoma cells and sarcoma cells, which when transplanted separately as metastases continued to exhibit and demonstrate their individual characters. (The full report will be published in the *Journal of Cancer Research*.)

#### SARCOMA OF THE STOMACH. GEORGE M. CURTIS AND P. A. DELANEY.

Primary sarcoma of the stomach is rare, although more than 250 cases have been reported. It occurs once in 2,260 necropsies (Hosch: *Deutsche Ztschr. f. Chir.* **90**:98, 1907) and constitutes between 1 and 2 per cent of the malignant growths of the stomach. Even higher incidences are reported (Fenwick: *Lancet* **1**:463, 1901). Smithies, however, found but 4 cases in "a study of 921 operatively and pathologically demonstrated instances of gastric cancer" (Cancer of the Stomach, Philadelphia, W. B. Saunders Company, 1916). Unlike carcinoma, it affects the sexes equally (Hesse: *Zentralbl. f. d. Grenzgeb. d. Med. u. Chir.* **15**:550, 1912). On the average, the onset is between the ages of 44 and 45, and the greatest frequency is between 40 and 60. The youngest patient, a child aged  $3\frac{1}{2}$ , had a spindle cell sarcoma (Finlayson: *Brit. M. J.* **2**:1535, 1899). The first authentic case was reported by Virchow: a round cell endogastric sarcoma of the pyloric region in "ein junges Mädchen" (*Die krankhaften Geschwülste*, ed. 2, Berlin, 1864). Recently, several sporadic cases have been reported; for example, Brander's (*Brit. M. J.* **1**:139, 1927), which was soon followed by three others (*Brit. M. J.* **1**:393, 632 and 845, 1928). Without doubt, a large number of similar cases remain unreported. It is also probable that on careful microscopic study several cases among those thought to be carcinoma will prove to be sarcoma. The most recent case I have found is that of Pember-ton, an exogastric fibrosarcoma of the pyloric region (*Proc. Staff Meetings Mayo Clinic* **4**:17, [Jan. 16], 1929).

The etiology and histogenesis of this disease are obscure. Gastric ulcers have been unnecessarily accused, likewise trauma. There is evidence however, of sarcomatous degeneration of benign gastric myomas, as in von Eiselsberg's case as studied by Nauwerck (*Arch. f. Chir.* **54**:568, 1897). Other similar cases are reported (Konjetzny: *Ergebn. d. Chir. u. Orthop.* **14**:256, 1921). Sarcoma originates most frequently in the submucosa, less frequently in the muscularis and rarely in the mucosa or subserosa (Hesse).

Grossly, three forms are described (Konjetzny). The exogastric protrudes from the wall of the stomach in varying degrees; stalked, broad-based and intermediate forms are described. The intramural forms are usually infiltrating. The endogastric forms are more commonly fungous and ulcerating. Multiple forms are described.

The greater curvature, posterior wall, pylorus and lesser curvature are the common locations involved, in descending order of frequency. The ostia of the stomach are rarely involved (Lofaro: *Arch. gén. de chir.* **4**:8, 1909). This is of clinical importance in connection with the infrequency of obstruction resulting from these neoplasms.

Hesse carefully analyzed the microscopic character of 144 cases. The round cell forms predominate, particularly lymphosarcoma. It is often difficult to differentiate these forms from one another and from regional lymphocytic tumors. There follow in order spindle cell sarcoma, myosarcoma, mixed fibrous and muscular forms, mixed cell sarcoma and then rarer varieties, such as angiosarcoma.

Metastases are not so frequent as with carcinoma, occurring in about 37.5 per cent of the cases, and are usually of the lymph nodes or liver (Aschoff: *Path. Anat.* **2**:735, 1923). Myosarcoma may form enormous cystic metastases in the liver. In Hosch's case, the liver weighed 10,900 Gm. and contained many



large cysts. Secondary sarcoma of the stomach is considerably more rare than the primary form (Ziesché: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 20:377, 1909).

Malignancy of the stomach is not always accompanied by even moderate symptoms of gastric disease. This applies particularly to certain cases of extrinsic sarcoma, as in the case reported. In this case there were practically no gastro-intestinal symptoms during the disease; there was, however, a marked secondary anemia, and in the investigation of its cause the tumor was discovered at fluoroscopy. Resection of a leiomyosarcoma of the pyloric region was followed by recovery and a restitution of the blood.

A housewife, aged 59, came to the surgical clinic on June 11, 1928, because of pain in the right wrist, subsequent to a Colles' fracture sustained three months previously. At that time there were no abdominal symptoms. Her appetite was good, the bowel movements were regular and so far as she knew the stools were normal. There was no abdominal distress or flatulence. There was no history of cancer in the immediate family; however, there was severe tuberculosis. During the preceding four months, the patient had lost about 15 pounds (6.8 Kg.). Results of examination of the chest and films of the chest were essentially negative, although there was a history of an old asthmatic bronchitis. The urine was normal, and the blood pressure was 150 systolic and 90 diastolic.

Owing to some dyspnea and palpitation which had become worse during the previous two months, until it was noted even on slight exertion, she was referred to the cardiac clinic for further study. There a severe anemia was disclosed, with 8.6 Gm. of hemoglobin per hundred cubic centimeter of blood and 3,320,000 erythrocytes. The leukocyte count was 6,600, with a slight lymphocytosis and evident but moderate poikilocytosis. The cause of the anemia was obscure.

During the ensuing month the patient became weaker, lost more weight and was finally forced to remain in bed. Vague symptoms such as heart-burn and mild epigastric distress appeared, and her appetite diminished. The anemia increased, and there was marked poikilocytosis, anisocytosis and achromia. The lymphocytosis persisted as the leukocyte count became 10,800. Then rather suddenly a severe diarrhea began with nausea and vomiting. The latter may have been due to medication. She became so exhausted that it was necessary to take her into the hospital on a stretcher.

Again a severe secondary anemia was found, the cell count revealing: red blood cells, 2,000,000; white blood cells, 9,600; neutrophils, 68 per cent; lymphocytes, 26 per cent; reticulocytes, 6.6 per cent, monocytes, 4 per cent, basophils, 1 per cent, and eosinophils, 1 per cent. There was a definite variation in the size and shape of the erythrocytes, and in their staining qualities. The hematocrit reading was 22. The oxygen capacity of the blood was 7.6 per cent by volume. Both qualitative and quantitative van den Bergh tests were negative. The fragility test was normal. An Ewald meal revealed 10 degrees of free acid, and blood was found in both the gastric content and the stools. This led to fluoroscopy in an endeavor to determine the source of the blood loss. Rather surprisingly a large filling defect of the lesser curvature at the pylorus was found, with a palpable mass and considerable rigidity of the adjacent wall of the stomach. The peristaltic waves did not pass through this area, and yet the stomach emptied rapidly and completely. Films clearly revealed the defect and suggested a fungating neoplasm of the lesser curvature, above the pylorus, without obstruction.

Owing to the motility of the stomach and the absence of demonstrable metastases, particularly in the roentgenograms of the chest, it was thought that the neoplasm was probably resectable, and operation was advised. The patient was given two preoperative blood transfusions, 500 cc. of citrated blood, type IV, being used. The second was followed by a rather severe reaction. On July 26 the abdomen was opened, and a resectable tumor was discovered at the pylorus. The tumor was ovoid, about 4 inches (10.16 cm.) in length, and was attached by a broad base to the anterior wall just below the lesser curvature. The omentum was firmly attached to its anterior surface, and the region of attachment

was hemorrhagic. No metastases were found. Resection was followed by a retrocolic Reichel-Polya gastro-enterostomy without an entero-enterostomy between the afferent and efferent loops.

Recovery was complicated by rather severe vomiting for about a week. This was controlled by continuous gastric aspiration with lavage, Ringer's solution by hypodermoclysis and intravenous dextrose. At the end of six weeks, fluoroscopy revealed a normally functioning gastro-enterostomy. At the time of presentation, seven and one-half months after the resection, there was no evidence of recurrence or metastases, and the blood was essentially normal: hemoglobin, 18 Gm per hundred cubic centimeters, and 4,400,000 erythrocytes.

The portion of the stomach resected was 15 cm. in length and weighed 270 Gm. A firm, ovoid tumor, 11 by 7.5 by 6 cm., projected from its anterior surface, 5 cm. from the pylorus (fig. 1). The base of this tumor was broad, 5 by 6 cm., and lay 1 cm. below the lesser curvature and 6 cm. above the greater curvature. There was almost no stalk. Numerous fibrous adhesions appeared on the posterior surface of the stomach. The veins of the smoother anterior surface were distended. The pyloric opening readily admitted the index finger. Within the stomach, the



Fig. 1.—The portion of the stomach resected, showing the exogastric sarcoma. The pylorus is at the left, the greater curvature is below.

rugae and mucosa were normal save at the attachment of the tumor. This irregularly ovoid area, measuring 5 by 3 cm., was reddened, 7 mm. in thickness and of a firm cartilaginous consistency. Three ulcerated openings appeared on its surface from which sinuses led to the central portion of the tumor.

The external surface of the tumor was covered by glistening serosa save on the anterior surface where the omentum was attached. Here were numerous fibrous adhesions and irregular subserosal hemorrhages. The surrounding veins were dilated. On palpation the tumor mass was cystic, and its wall was of uneven consistency. When incised, an irregular central cavity was disclosed, containing about 15 cc. of fluid blood, blood clots and necrotic material. The cavity measured 5.5 by 2.5 by 2 cm. Its wall was lined by a grayish, blood-stained, necrotic material, and was formed by irregular masses of the tumor substance.

Pieces for microscopic study were taken from the junction of the tumor and the stomach wall, the gastric mucosa adjacent to the tumor, the cyst lining and from various portions of the tumor. Sections were prepared and stained with hematoxylin and eosin, Mallory's stain, phosphotungstic acid-hematoxylin, aniline acid-fuchsin with methyl green or Wright's as a counterstain, iron hematoxylin and Mayer's mucicarmine.

The main portion of the tumor was composed of elongated spindle-shaped cells containing fibrils of various sizes and having ovoid nuclei with evenly scattered chromatin and rounded ends (fig. 2). Mallory's stain revealed their noncollagenous character, and the myoglia fibrils were particularly well demonstrated by phosphotungstic acid-hematoxylin. Branching fibrous trabeculae, definitely collagenous, separated the tumor into irregular areas of parallel cells. These were of three general types. In one the typical nuclei predominated, mitoses were frequent and there was but little differentiation. This area was characterized by rapid proliferation. In a second area the individual cells were more evident, mitoses were not so frequent and myoglia fibrils were readily visible (fig. 2). The cells showed more definite differentiation. The third areas presented varying degrees of intergradation between the first two.

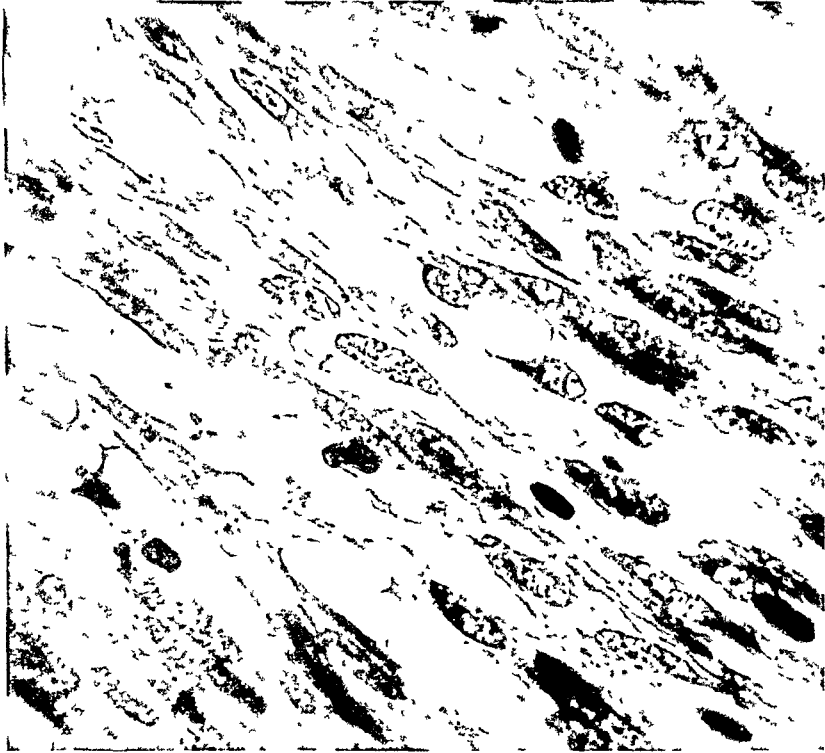


Fig. 2.—High power of a characteristic section presenting the typical tumor cells in an area in which differentiation predominated.

The cavity of the tumor was lined by necrotic tissue, with old hemorrhage. There was no epithelial lining. At its margin the tumor was invading the mucosa. Originating within the muscularis, the groups of spindle-shaped cells had destroyed the overlying muscularis mucosa and were extending into the deeper portion of the mucosa. The gastric mucosa adjacent to the tumor was invaded by a number of leukocytes. Parietal cells were relatively frequent. The interglandular connective tissue was increased.

Ribbert objected to the use of the term sarcoma in connection with neoplasms of muscular origin. McGill's (*Internat. Monatschr. f. Anat. u. Physiol.* 24:209, 1907) work, however, demonstrated that smooth muscle and fibrous connective tissue originate from similar mesenchymal cells.

The tumor was a slowly growing leiomyosarcoma of the anterior surface of the stomach near the pylorus, originating within the muscularis and without demonstrable metastases.

## DISCUSSION

FRANK SMITHIES: Sarcomas of the stomach arise in the ulcer-bearing portions on either wall, and their metastasis is peculiar. With carcinoma there is a disappearance of peristalsis, but with sarcoma the peristalsis is maintained. Hemorrhage is not an important factor. With these points in mind, carcinoma can be eliminated; however, cysts and syphilis of the stomach must be considered.

## ACUTE YELLOW ATROPHY OF THE LIVER FOLLOWING ADMINISTRATION OF OXYL IODIDE. S. D. ANDERSON.

Oxyl iodide is a therapeutic product said to be composed of "one part of iodine to five parts of phenylcinchoninic acid, two parts of the latter in chemical union with one part of iodine." This drug, therefore, contains 83 per cent of cincophen and 17 per cent iodine. Reports are found in the literature of eight fatal cases of toxic jaundice following the administration of cincophen or some of its derivatives. The patients examined post mortem died of acute yellow atrophy of the liver, but only two reports are reported in full.

A woman, aged 48, had complained of stiffness, swelling and soreness of the joints of the fingers of both hands. Oxyl iodide in doses of 3 grains (0.195 Gm.) three times a day was prescribed over a period from May, 1928, until January, 1929. During this time, she took approximately 600 (3 grain) tablets. In the latter part of January, edema of the face and the extremities and moderate jaundice developed. She became irrational at times. The urine was greatly reduced in quantity, had a specific gravity of 1.024 and contained albumin and many hyaline and epithelial casts, acetone and diacetic acid but no sugar. The blood showed: red blood cells, 3,600,000; hemoglobin, 62 per cent and leukocytes, 9,200.

A postmortem examination was made twelve hours after death and revealed acute yellow atrophy of the liver, ascites, edema of the lungs, generalized edema of the subcutaneous tissues, and petechial hemorrhages in all of the viscera.

The liver weighed 450 Gm., was flabby, its surface irregular and its color mottled purplish and yellowish brown. The surfaces made by cutting showed numerous circumscribed, raised, yellow areas from 6 to 10 mm. in diameter, against a dark red-brown background. The kidneys were yellow-gray, the cortex swollen and the cortical markings indistinct. The microscopic examination of the liver showed areas of necrosis and hemorrhage beginning about the central veins and extending for varying distances into the lobule. Many entire lobules and groups of adjacent lobules were completely necrotic, and the connective tissue framework of the liver with its bile ducts was collapsed. The bile ducts, therefore, appeared numerous and were separated by loose connective tissue in which hemorrhage had occurred. The kidneys showed cloudy swelling, fatty degeneration and some necrosis of the tubular epithelium. There were no noteworthy changes in the other organs except as indicated in the anatomic diagnosis.

## DISCUSSION

R. H. JAFFÉ: It would seem that susceptibility of the liver must be some factor here, because cincophen derivatives are used extensively in medicine without untoward effects. Is it possible that some other cause has induced the changes of the liver?

E. R. LONG: Have animals been tested to see if the compound has toxic properties?

EDWIN F. HIRSCH: Were qualitative or quantitative chemical tests made?

A CASE OF RHINOSPORIDIUM SEEBERI IN A RESIDENT OF THE UNITED STATES.  
MARY C. LINCOLN and STELLA M. GARDNER.

This paper appears in full in this issue, p. 38.

## DISCUSSION

EDWIN F. HIRSCH: The lesions illustrated resemble those of coccidioidal granuloma in certain respects.

## CLINICAL AND PATHOLOGIC ASPECTS OF APPENDICITIS. BERNARD PORTIS.

Appendicitis is the most frequent of all pathologic conditions of the abdomen. The rotation of the cecum during embryonic development explains the various positions which the appendix may assume.

Most of the 135 cases of acute appendicitis were apparently hematogenous, and about 25 were associated with some form of infection of the upper respiratory tract. A local origin from a small ulceration, however, was also considered a cause. The earliest microscopic changes are hyperplasia of the lymph follicles and raising of the lining epithelium by a serofibrinous exudate. Somewhat later the exudate infiltrates the wall or enters the lumen. Gangrene and perforation may then occur. Resolution is the most favorable outcome, but most cases which have reached the suppurative stage rarely subside.

Many of the patients operated on for acute appendicitis were seen late after the onset and frequently had been subjected to drastic purging. In spite of this, there were only four deaths from peritonitis. The clinical features were somewhat dependent on the age of the patients. In young children the symptoms were bizarre, while in older children the symptoms were similar to those of adults. The onset was never sudden, but developed to an acute intensity in several hours. In 75 per cent of the cases the pain was generalized and localized only to the right lower quadrant after several hours. Backache was severe when the appendix was retrocecal. Gastro-intestinal distress was present in all cases. In a few it manifested itself simply by anorexia, while nausea and vomiting occurred in 77 per cent. Fever was present usually at the end of twenty-four hours. The leukocytes of the blood were increased usually to from 15,000 to 20,000. There were, however, four patients with gangrene of the appendix without leukocytosis. Localized tenderness was constant, but rigidity was often absent.

Chronic appendicitis is usually not inflammatory but is produced by adhesions and kinking of the appendix with interference to the normal peristalsis. The symptoms may simulate any of the chronic inflammatory conditions of the gastro-intestinal or bile tract.

## Book Reviews

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DEGENERATION AND REGENERATION OF THE NERVOUS SYSTEM. By S. RAMÓN Y CAJAL, M.D., F.R.S., Director of the Instituto Cajal, Madrid, Honorary Professor of Pathology in the University of Madrid. Translated and edited by Raoul M. May, Ph.D. (Harv.), D. ès Sc. (Paris). Two volumes. Pp. 769, with 317 illustrations. New York: Oxford University Press, 1929.

This great work, which was published in Spanish in 1913 and 1914, is described by the author in his preface to the present translation as practically "unpublished in Europe and North America." As a testimonial to the distinguished author, on the occasion of his receipt of the Nobel Prize, the physicians of the Argentine Republic asked permission to publish at their own expense a memoir containing his researches, and these two volumes were prepared for that purpose. It is not a reprint of previous publications, but an entirely new work, representing much additional research directed especially toward this end. Nearly all the copies of the Spanish edition were distributed to the South American subscribers; hence, the work has been difficult of access by the rest of the world. The translator and the Oxford Press have performed a great service and both have done their work extremely well. An excellent portrait adds a welcome personal touch.

The book contains the ripest fruits of a wide experience in a difficult and controversial field. The theories of nervous degeneration and regeneration are interwoven with those of the histogenesis of nerve fibers, and the work opens with a sketch of the historical development of these ideas with a critical analysis of the evidence. These controversies may be regarded as closed so far as the major issues are concerned.

"The doctrine of the neurone, intimately connected in the pathological field with the theory of continuity, came out of this new crisis strengthened and victorious. Instead of finding, in the field of nervous regeneration, insuperable difficulties, it found, on the contrary, new and peremptory demonstrations, in whose light not a few of the enigmatic phenomena of the morphology and growth of nervous protoplasm are beginning to be understood."

These words at the close of the first chapter indicate the general point of view, and the remainder of the work is devoted chiefly to factual description of the author's own preparations, with full citation of the work of others. It is impossible here to summarize these observations, which are presented in a clear and convincing way. Chapter XVI, at the close of the first volume, summarizes the "General Theoretical Interpretation of the Phenomena of Nervous Regeneration" in a succinct statement of the leading facts and their bearing on the author's theory of neurotropism.

The second volume is devoted entirely to degeneration and regeneration of the nerve centers, including the sensory and sympathetic ganglions, the spinal cord and the brain. This is of special interest to neuropathologists, for it records much experimental work not widely known in this country. As in the first volume, the citations of the literature are full, critical and extremely helpful.

The doctrine of neurotropism is the most important theoretical conclusion of the entire program, and constant references to it are made throughout the book. This conception is founded on the belief that in the peripheral nerves there is a symbiotic relation between the axon of the neuron and the sheath cells, and in the nerve centers, including all peripheral ganglions, neuroglia and satellite cells are related to neurons in a somewhat similar way. In the second volume (p. 459), he elaborates the hypothesis of the disequilibrium of the neuroneuroglial symbiosis.

"On various occasions we have pointed out the fact that the neurone, far from living independently, becomes dynamically and trophically associated with certain cells of a special nature, among which we include the *protoplasmic neuroglia* of

the centers, the *satellite cells* of the ganglia (*amphicytes* of v. Lenhossék) and the *cell of Schwann* of the nerves. The two categories of elements are mutually serviceable, and there is established between them something like a symbiosis comparable to the well-known symbioses of fungi and algae to form lichens, or of the hydra and its chloroplasts.

"In a normal state, that is, when the reciprocal actions are in equilibrium, the satellite cells are few. They abstain from proliferating and they respect the neuronal morphology. This quiescence is perhaps due to the paralyzing action of some principle which is liberated, under normal conditions, by the young and robust neurones. When these become fatigued, however, or when they weaken or die, the antimitogenic check is moderated or suspended, and the satellite cells therefore multiply and press upon the periphery of the neuronal soma, forming in it pits and even holes, handles, fenestrations, etc. Moreover, the growing pressure of the satellite cell, or of the daughter cells proliferated from it, also brings about, through a mechanical or chemical stimulus, more or less important neoformative processes."

In the regeneration of peripheral nerves it is demonstrated that the cell of Schwann is not necessary for the genesis and growth of the axons. Yet the proliferation of these cells plays a significant part—indeed, a necessary part—in the regenerative process.

"The nervous reunion of the peripheral stump and restoration, without physiological errors, of the terminal nerve structures, are the combined effect of three conditions: the neurotropic action of the sheaths of Schwann and terminal structures; the mechanical guidance of the sprouts along the old sheaths; and, finally, the superproduction of fibers, in order to ensure the arrival of some of them at the peripheral motor or sensory organs" (p. 371).

In pathologic states of the ganglions and the central nervous system all the satellite cells and certain glial elements, necrosed or degenerating neurones, exudates with their leukocytes, etc., have some stimulating or neurotropic influence. But none of these have the potency of the proliferating cells of Schwann and, for this and other reasons, regenerative activities in the nerve centers, which are described in great detail, are abortive so far as restitution of normal function is concerned.

What may be the real nature of the reconstructive neurotropic influence is not revealed by any evidence so far available. Cajal writes (p. 392):

"It is difficult, in the present state of knowledge, to imagine what is the nature of the stimulating substance. As a tentative hypothesis we have supposed that the substance contained in the sheaths of Schwann of the peripheral stump should be conceived, not as a fixed, quiescent principle, capable of being neutralized like an alkali by some acid substance within the cone of growth, but as a ferment or catalytic agent which stimulates the assimilation of the axonic protoplasm and which does not become used up while acting on the nervous protoplasm."

In the earliest stages of regeneration, while the axonal sprouts are pushing out without guidance by neurotropic or other influences, the activity which they manifest is regarded (following Heidenhain) as due to an intrinsic histodynamic impulse which is a growth process not dependent on any specific material substance or soluble enzyme. This active metabolism of the early axonic sprouts seems to the reviewer to be related to the physiologic gradients of Child, both in its intrinsic nature and in its reactions to the surrounding medium. This applies also to the neurotropic influence of cells of Schwann, satellite cells, etc., in later stages of regeneration. Active metabolism excited by trauma, or otherwise, gives to the activated regions a physiologic dominance the mechanism of which is not fully understood but the manifestations of which are sufficiently similar to the phenomena described by Child in nonnervous protoplasm to justify further examination from this point of view.

The work of Cajal and his co-workers has led to a renaissance of neuropathology, and the further development cannot now be forecast. These volumes will do much to hasten this development in all English-speaking countries.

OLD AGE. THE MAJOR INVOLUTION. THE PHYSIOLOGY AND PATHOLOGY OF THE AGING PROCESS. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. Price, \$3. Pp. 199, with 29 illustrations. New York: Paul B. Hoeber, 1929.

The Wesley M. Carpenter Lecture of 1928 (Bull. New York Acad. 4:1006, 1928; New York State J. Med. 28:1349, 1928) forms the nucleus of this monograph. After the delivery of the lecture and its publication, the many requests for reprints indicated that the conception of old age advanced in the lecture was arousing a good deal of interest. This central conception remains unchanged, but additions and alterations have been made to clarify and strengthen the conception and the conclusion to be drawn from it. Most of the new matter consequently relates to involution as a physiologic process and function, because the central idea in this discussion of old age is that it should be regarded as essentially physiologic and as a normal major involution and not as a pathologic process. In the preface, the author states that "to his surprise a certain minority of his correspondents, while accepting the view put forward as rational and based on scientific facts, expressed themselves as 'having been depressed' by the philosophic conclusions inevitably deducible from such a view point." Just the opposite result was in the writer's mind—"the presentation of a rational workable philosophy of old age as an antidote to the modern futilities of life-extension of the individual to extreme limits and of possible rejuvenation." The first third of the book deals with the evolution and maturity of the "human machine," and the rest with old age—the major involution—under the following headings: The Functional Changes of Senescence; The Picture of Fully Developed Senility; The Primary Tissue Changes of Senescence; The Secondary Pathologic Changes of Old Age; The Concentration of Disease in Different Life Periods; Termination of the Involution Process in Normal Death; Pathologic Death; Theories of Senescence; Extension of the Life Limit; Rejuvenation; A Philosophy of Age. As perhaps might be expected under the circumstances, man as distinguished from woman rather monopolizes both the text and the illustrations, but it is made clear that the same general principles apply in both cases. The discussion of the normal limits to the duration of life is illuminating. The book is readable and instructive. The style is vigorous. The reasons for regarding old age as essentially the result of a normal physiologic process are set forth convincingly, and the significance of this conclusion in one's outlook on life is indicated clearly. The pathologist teaches a philosophy of life that will commend itself to the intelligent reader.

A MANUAL OF HELMINTHOLOGY MEDICAL AND VETERINARY. By H. A. BAYLIS, M.A., D.Sc., Assistant Keeper, Department of Zoology British Museum. Price, \$10. Pp. 303. New York: William Wood & Company.

Interest in parasitology has been widely aroused during recent years, and medical and veterinary men are more and more realizing the true importance of the affects on public health and on that of the domestic animals as caused by the flatworm, tapeworms and roundworms. Parasitology has formerly been considered to be of importance only to the tropics and subtropics; now its importance is recognized in all parts of the world. At this critical time this handbook of helminthology appears and will find a ready demand. It is broadly limited in its scope to those helminthes affecting man and the animals with which he may come in contact, including nearly all parasites of man and the domesticated animals of the world. This is particularly useful in this era of international travel and commerce, because one may at any time encounter forms of parasites new to one's own country or recently introduced. This book will help one to identify them.

It is written in a clear concise style with sufficient explanation to allow any educated man to use it successfully even though he lacks in knowledge of parasitology. The 200 figures aid a great deal in ready understanding. The information is reliable, and there is much evidence that the author has often turned to the original source material for information or illustration.



The classification used is the latest and best available, while in many instances the better known synonyms are also given. Poche has been followed in the classification of the trematodes and cestodes. It is questionable whether his larger groupings will find favor with parasitologists, but in many instances it is a decided improvement over older classifications, and it offers those generic and specific names which are most nearly in accordance with the international laws of nomenclature. Introductions and explanations are provided for each of the three divisions, the trematodes, the cestodes and the nematodes, while every smaller division is carefully defined. A general index and an index of hosts and their parasites greatly enhance the usefulness of this book.

It is a good textbook, but the price will prevent its general adoption for student use. However, it should find sale and be used extensively by the professions because it is an excellent reference book, a most worthy addition to the library of physicians, veterinarians, public health workers, parasitologists and zoologists.

The publishers have provided first quality paper and presswork in an attractive and substantial binding.

**COLLOID CHEMISTRY. THEORETICAL AND APPLIED.** By Selected International Contributors. Collected and Edited by Jerome Alexander. Vol. 2. Biology and Medicine. Price, \$15.50. Pp. 1,029. New York: The Chemical Catalog Company, 1928.

It is a fact, recognized by all who are familiar with the advances of modern science, that the more extensive and complex science becomes, the more narrowly do its devotees restrict themselves to highly specialized fields. This is especially true in the biologic sciences, in which theoretical advances have lagged far behind experimental observation and in which, consequently, one finds few of those great generalizations which serve to collect and coordinate isolated facts. The present tendency to explain vital processes by means of chemical and physical laws finds its greatest justification in the great strides which have been made in biology and medicine by the application of physicochemical methods. The present volume emphasizes the relationship between colloid chemistry and biology. Even the most casual reader of this book cannot fail to be impressed by the wide variety of contacts between the two fields, as evidenced by the titles of the papers presented. Thus one finds papers ranging from such general topics as proteins, enzymes, cell structure, protoplasm, fertilization, and micro-organisms to the more specifically medical provinces of serology, tuberculosis, malignant tumors, immunity and pharmacology. One cannot help feeling that colloid chemistry is the link which connects the various biologic sciences and that it represents the borderland not only between the various biologic sciences but also between those and the physical sciences. At the same time one is led to hope that future advances in this border field will lead to important clues concerning the structure and functional activity of protoplasm itself.

This volume, like its predecessor, consists of papers by selected contributors, each paper being a resumé of work done by the author and others in that particular field. The authors and their subjects have been chosen so as to be representative of the field covered. Besides containing numerous references to the original literature, each paper contains, in footnotes, comments by the editor and references to other papers both in this volume and in the first volume of this series, which deals with the more fundamental aspects of the subject. This book will prove a revelation to those medical students who have acquired the idea that there really is some connection, however mysterious, between colloid chemistry and medicine. It should prove valuable to those investigators who are anxious to know what contributions, if any, colloid-chemical methods may be expected to make to their particular fields. And to the general reader of biology and medicine, it should prove especially interesting as an indication of the trend of modern biologic thought.

# ARCHIVES OF PATHOLOGY

VOLUME 8

AUGUST, 1929

NUMBER 2

## MUCOID DEGENERATION OF THE OLIGODENDROGLIA AND THE FORMATION OF FREE MUCIN IN THE BRAIN\*

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AND

EVELYN STEVENS, M.S.

CHICAGO

In 1923, Grynfeldt,<sup>1</sup> on studying the central nervous tissues of persons with senile dementia, paralysis agitans and Wilson's disease, found peculiar polylobate patches in the white matter which gave the characteristic histochemical reactions of mucin. At that time, he termed these mucin bodies mucocytes, and thought that they arose from degeneration of microglia cells. Later, Grynfeldt, Pélissier and Pagés<sup>2</sup> demonstrated in their experimental material that a progressive degeneration of the oligodendroglia cells resulted in the accumulation of intracellular mucin, which, on disintegration of the cells, was liberated free into the tissue and tended to coalesce.

The resulting free mucin was identical with the grapelike areas of disintegration reported by Buscaino<sup>3</sup> in 1922. He believed that they had their source in degeneration of myelin sheaths and, less possibly, in degeneration of ganglion cells. Buscaino doubted the mucoid nature of the material and termed it "substance X."

Grynfeldt<sup>4</sup> later produced ependymal lesions in dogs by means of injections of histamine and formic acid and found that progressive degeneration of the subependymal glia cells produced typical grapelike areas, and that the mucin thus produced was discharged into the ventri-

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\* Submitted for publication, May 17, 1929.

<sup>2</sup> From the Division of Neurology, Department of Medicine of the University of Chicago and the Douglas Smith Foundation for Medical Research.

1. Grynfeldt, E.: Mucocytes et leur signification dans les processus d'inflammation chronique des centres cérébraux spinaux, *Compt. rend. Soc. de biol.* **89**: 1264, 1923.

2. Grynfeldt; Pélissier, and Pagés: Demonstration sur la dégénérescence mucocytaire dans les centres nerveux, *Bull. Soc. d. sc. méd. et biol. de Montpellier* **46**:260, 1924.

3. Buscaino, V. M.: Le cause anatomopatologiche della precoxe, *Riv. di patol. nerv.* **25**:147, 1920 (cited after Ferraro).

4. Grynfeldt, E.: Lésion de l'épendyme dans la dégénérescence mucocytaire des centres nerveux, *Bull. Soc. d. sc. méd. et biol. de Montpellier* **8**:450, 1927.

cles and could be demonstrated in the spinal fluid. Simon<sup>5</sup> repeated this experimental work and found the same mucoid degeneration of the oligodendroglia in the white matter and deep cortical brain layers. She also found free mucin in the perivascular spaces.

Bailey and Schaltenbrand<sup>6</sup> demonstrated that the acute swelling of oligodendroglia described first by Penfield and Cone,<sup>7</sup> in which the cytoplasm of these cells becomes swollen with a clear, nonstainable fluid, is identical with the mucoid degeneration of Grynfeldt. The acute swelling begins with a fragmentation of the short cell processes, a pyknosis and shrinking of the nucleus, and an increase of the cytoplasm by the imbibition of a nonstaining substance. Eventually, the nucleus is extruded and the cell completely disappears. By means of mucin stains, Bailey and Schaltenbrand demonstrated that the clear fluid filling the cytoplasm was in reality a mucin-like substance.

Bielschowsky<sup>8</sup> and others considered the substances staining like mucin purely as artefacts. Ferraro,<sup>9</sup> however, although not decisively stating that the so-called mucocytes were artefacts, believed that their pathologic significance was doubtful. His two arguments against the conception that they are degenerative products of oligodendroglia are that they can be found in normal brains and that, although the acute swelling of the oligodendroglia cells can be demonstrated easily, mucin cannot be stained in frozen sections. Ferraro could stain mucin-like substances only if alcohol had come in contact with the tissue; consequently he believed that an "alcohol sensitization" was necessary for the demonstration of the "substance X" as mucin. Furthermore, he did not deny the presence of mucin in glia cells or even oligodendroglia, but considered that it was present intracellularly only in phagocytic glia cells which were conveying the mucin from its origin in degenerated myelin sheaths to the blood vessels. That this material was present in oligodendroglia meant that these glia could become phagocytic or gitter cells, a conception which Ferraro<sup>10</sup> attempted to prove, but which has not been confirmed.

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5. Simon, A.: Étude d'histo-pathologie expérimentale sur la dégénérescence muqueuse de la névroglie, Thesis, Fac. med. de Montpellier, 1926.

6. Bailey, P., and Schaltenbrand, G.: Die Muköse Degeneration der Oligodendroglia, *Deutsche Ztschr. f. Nervenhe.* **97**:231, 1927. (See this paper for colored plates.)

7. Penfield, W., and Cone: Acute Swelling of Oligodendroglia, *Arch. Neurol. & Psychiat.* **16**:131 (Aug.) 1926.

8. Bielschowsky, M.: Review of Buscaino's Work, *Zentralbl. f. d. ges. Neurol. u. Psychiat.*, 1927, p. 604.

9. Ferraro, A.: Acute Swelling of the Oligodendroglia and Grapelike Areas of Disintegration, *Arch. Neurol. & Psychiat.* **20**:1065 (Nov.) 1928.

10. Ferraro, A., and Davidoff, L. M.: The Reaction of Oligodendroglia to Injury of the Brain, *Arch. Path.* **6**:1030 (Dec.) 1928.

## OBSERVATIONS

The human material that we studied consisted of so-called normal brains and pathologic brains in our laboratory collection from cases of uremia, cerebral arteriosclerosis, encephalomalacea, toxic and epidemic encephalitis, Schilder's disease and a variety of other conditions. Sections of tissue embedded in paraffin and celloidin and frozen sections were stained to demonstrate myelin sheaths, axis cylinders, fat, glycogen and connective tissue. The usual hematoxylin-eosin, toluidine blue and Hortega silver carbonate methods were also utilized. A composite

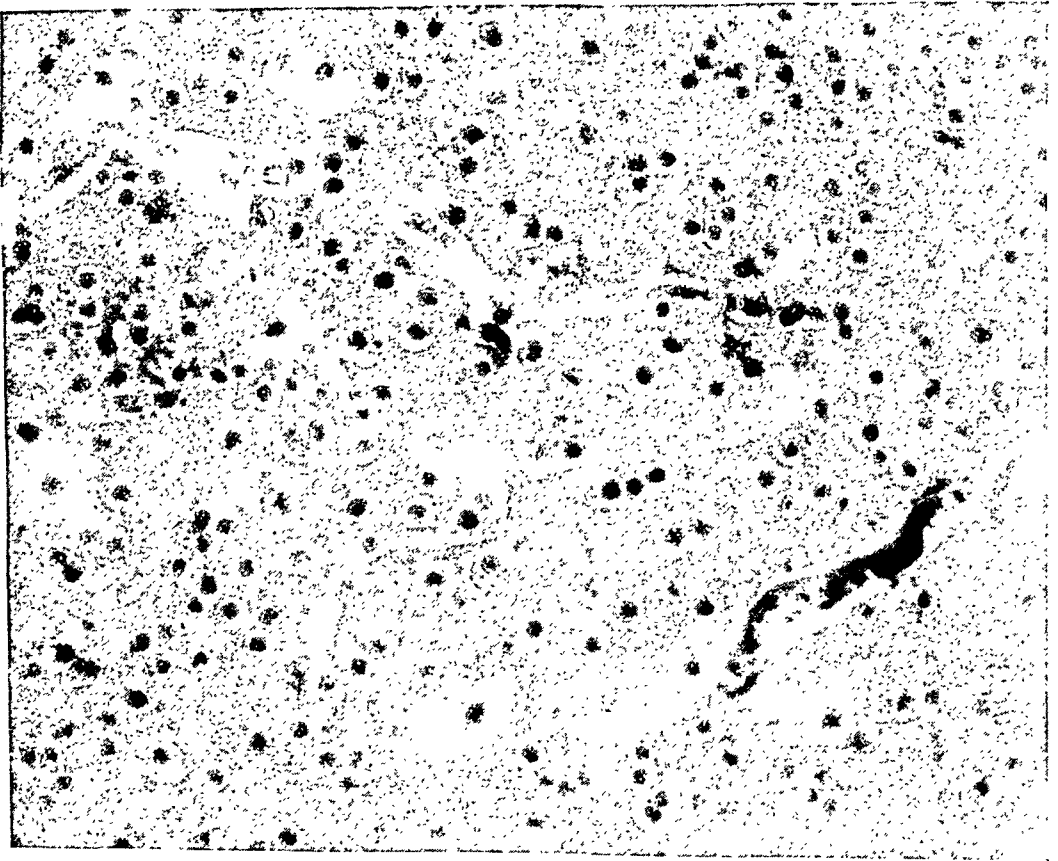


Fig. 1.—Proliferated, swollen oligodendroglia, frequently coalesced. The larger light areas represent mucin free in the tissue and perivascular. Mucicarmine stain;  $\times 390$ .

description of our observations with all methods and materials will be given.

In most of the brains studied, including the so-called normal ones, acute swelling of the oligodendroglia was found, which is a pathologic condition of a degenerative type. Using this criterion, then, one finds few "normal" brains, for although no important pathologic changes related to the cause of death may be present in the brain, various terminal states, such as fever, dehydration, anoxemia, anemia and agonal states, produce their effect. The oligodendroglia respond to the mildest of

noxious influences by means of active proliferation and acute swelling. These reactions may have a quantitative response to the severity of the toxic process. Therefore, the presence of swollen oligodendroglia and mucinoid degeneration of them in normal brains does not indicate that these changes are artefacts.

In acute toxic encephalitis,<sup>11</sup> for example, the oligodendroglia are massively increased in the white matter of the cerebrum and also as perineural satellitic cells in the cortex. They tend to form streams along the blood vessels, and to the inexperienced their small round nuclei

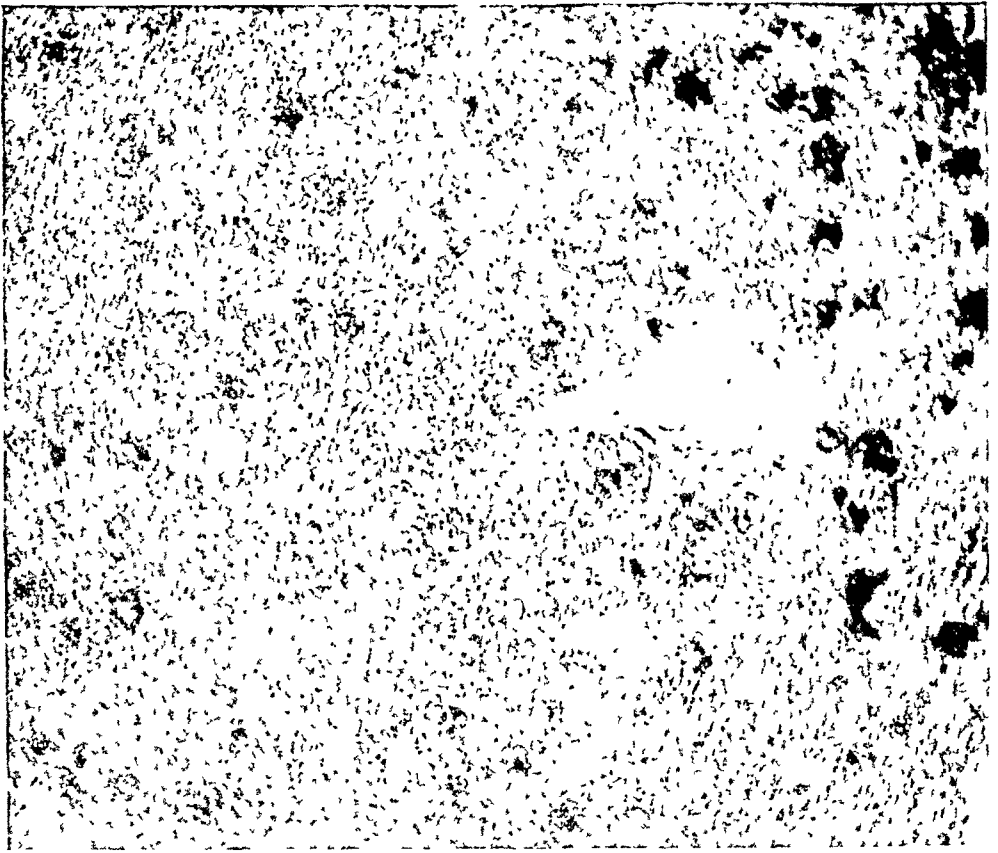


Fig 2.—Oligodendroglia filled with mucin. The lighter areas are spaces from which free mucin has dropped out of the tissue. Mucicarmine stain.

may even simulate a lymphocytic infiltration. When these proliferated cells swell, even in ordinary nuclear stains the small nuclei may be seen surrounded by a clear, white, circular zone (fig. 1). This appearance is often erroneously interpreted as pericellular edema, but the swelling is within the cell membrane.

In the attempt to stain this cytoplasm, silver impregnations reveal only a colorless fluid embedded in a faint argentophilic reticulum. Fat

11. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood, *Arch. Neurol. & Psychiat.* **20**:244 (Aug.) 1928.

is rarely demonstrated, although an occasional fat granule may be found. No active phagocytosis or formation of gutter cells by the oligodendroglia has been seen by us, although Ferraro contended that such a transition can be shown. Probably his observation represents a fatty degeneration of the cells themselves, although this in itself is extremely rare, being seen by us only once in encephalomyelitis<sup>12</sup> due to rabies vaccine in the form of fine intracellular granules. An attempt at the vital staining of experimentally injured brains of rats has never revealed an oligodendroglia containing dye granules, although the

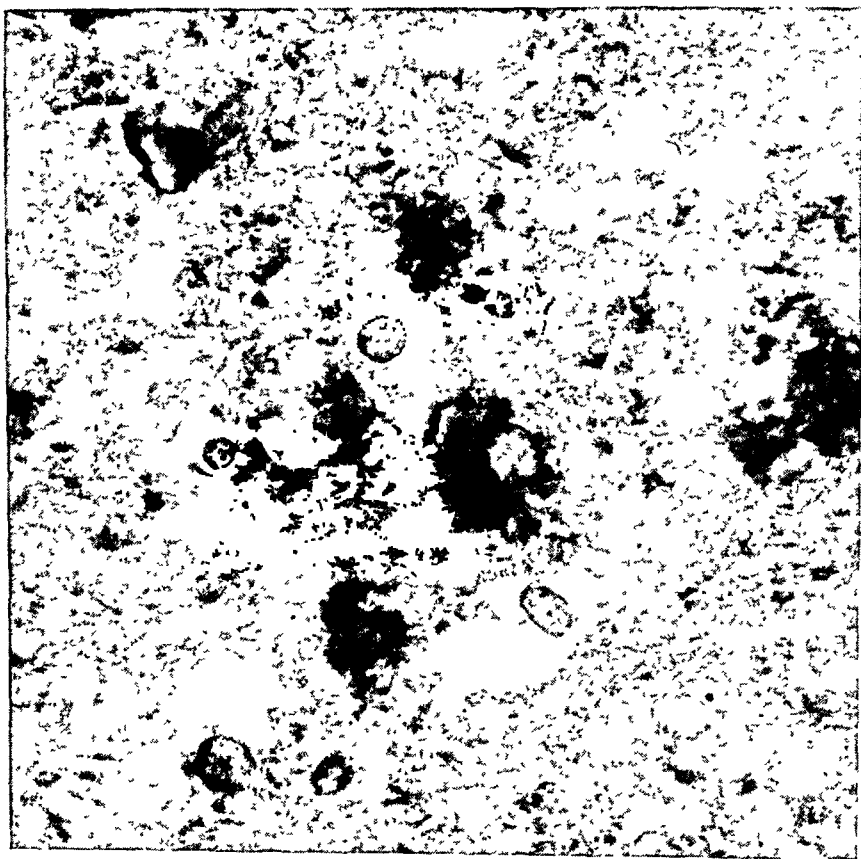


Fig. 3.—An oligodendroglia cell filled with mucin. Mucicarmine stain;  $\times 850$ .

microglia and their transitional stages to gutter cells contain the vital dye. Therefore, since a phagocytic property of these cells probably does not exist, the picking-up of material which distends the cytoplasm, such as mucin, probably does not occur.

The use of mucicarmine shows that the supposed colorless, swollen cytoplasm stains pinkish red (fig. 2). A metachromatic appearance is found with cresyl violet, and a homogeneous glassy-white appearance

12. Bassoe, P., and Grinker, R. R.: A Clinico-Pathologic Study of Rabies Vaccine Encephalo-Myelitis and Human Rabies, to be published.

with toluidine blue (fig. 5). This stainable substance first appears in an irregular perinuclear ring with delicate strands extending to the cell membrane. Later the mucin-like substance fills the entire cell and, as the cell becomes larger and its surface more irregular, the mucin follows its alteration in shape (fig. 3). The material is not glycogen, since no staining is obtained by Best's method, nor does treating the sections with saliva and subsequent staining of them with mucicarmine alter the appearance.

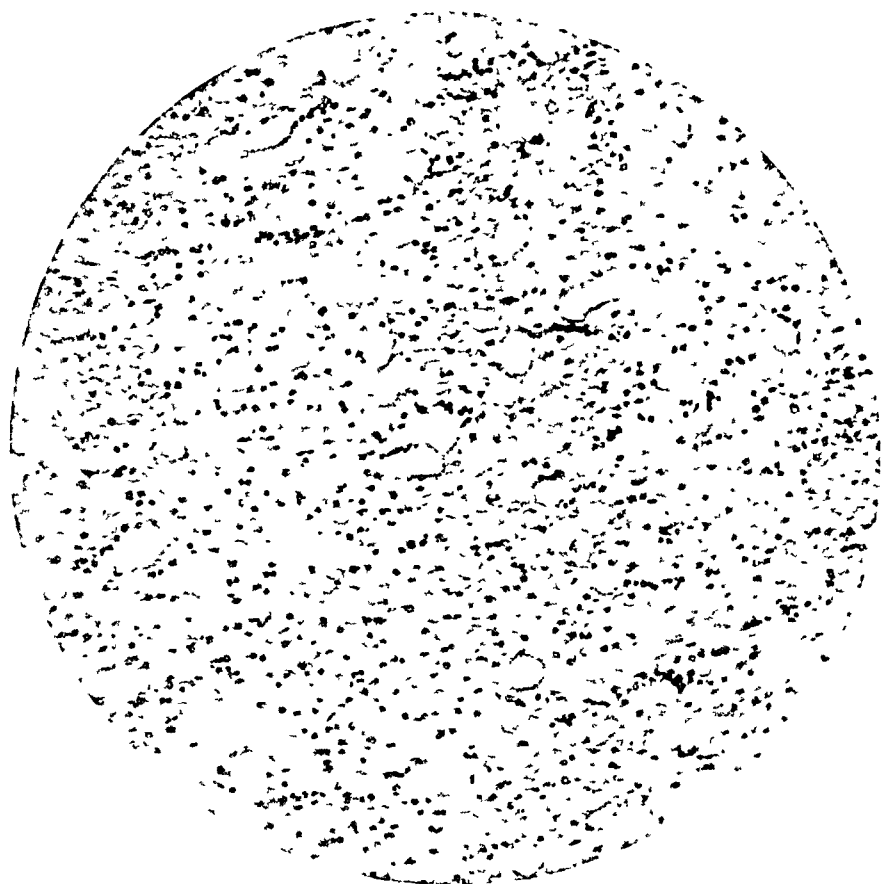


Fig 4.—Proliferated, swollen oligodendroglia. The white holes represent mucocytes and are not shrinkage spaces. Van Gieson stain.

The grapelike bodies of Buscaino are numerous. These are large clumps of material in irregular lobulated forms, which stain with mucicarmine. Smaller globules are also present in the tissue, as well as structures of irregular shapes in the midst of nerve fibers. Occasionally, a granular form is seen. The same substance is found in the perivascular and subarachnoid spaces and even within the vessel lumen. Within the grapelike bodies are many swollen oligodendroglia filled with mucin, some of which are only evidenced by a cell membrane, the nucleus being completely degenerated. Mucin clumps identical in shape and size

with clumps of glia cells can be seen, all the nuclei already extended. Coalescing of several oligodendroglia cells filled with mucin, before nuclear degeneration or loss of cell structure have taken place, may be followed to the complete absence of cells and the presence only of free mucin.

Where a globule of mucin is near the surface of the section, pressure on the cover slip results in its loosening from the tissue, leaving a hole. Many of these holes are found, in sections treated with ordinary

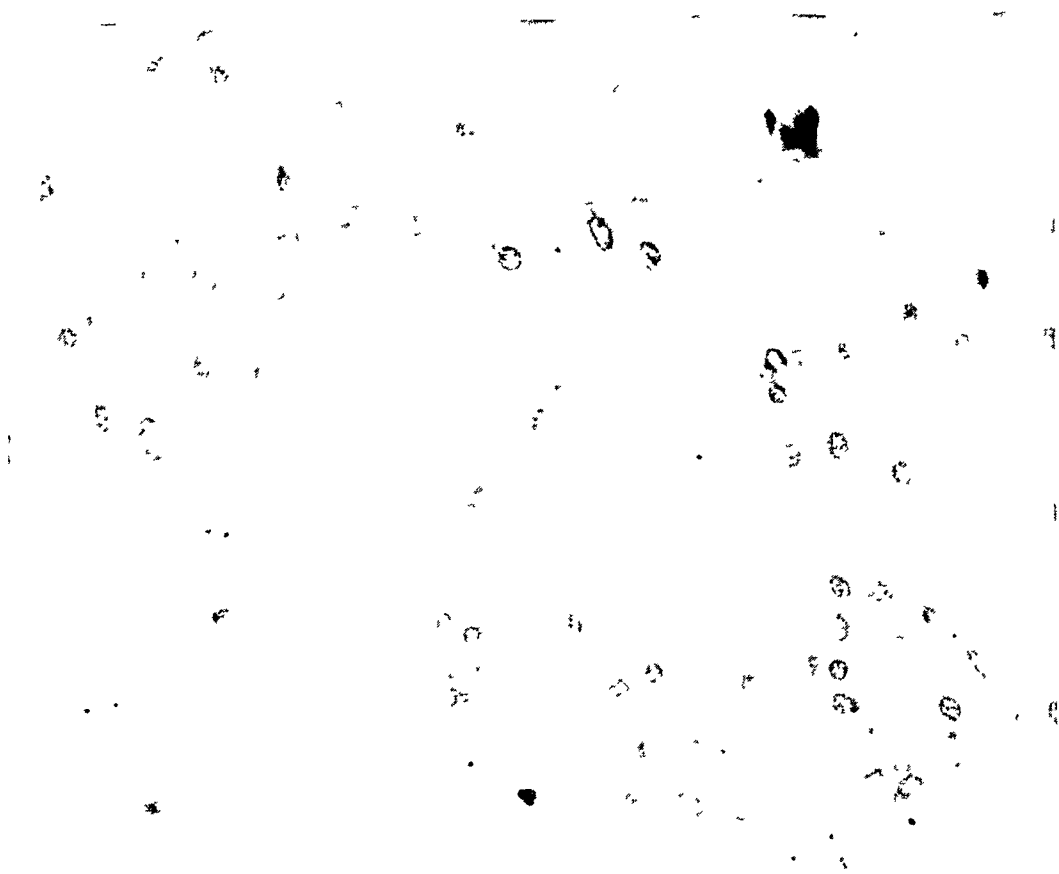


Fig. 5—Large, homogeneous, glassy globules of mucin. Toluidine blue;  $\times 470$ .

nuclear stains or with mucicarmine, unstained. They give a sievelike appearance to the section and have been erroneously called tissue spaces due to edema or shrinkage (fig. 4). However, in carefully dehydrated celloidin sections, such an appearance is not found normally. These holes and the stainless cytoplasm of swollen oligodendroglia represent spaces from which mucin has dropped out of the section. The substance is probably only loosely fixed in the cell or the tissue. Correspondingly, smearing the sediment from the bottom of the brain on a slide and staining for mucin shows clearly the globules of mucin which have simply dropped to the bottom of the dish.



Careful examination of the myelin sheaths reveals no evidence of their disintegration. When the mucocytes are found in the white matter, as they grow in size the fibers are simply pushed aside and compressed, but no degeneration is found. No other element, except the oligodendroglia cells themselves, gives any suggestion of partaking in the formation of mucin.

The important point of preparation of the substance X for staining as mucin is easily solved when we find that, without difficulty, mucin can be demonstrated on frozen sections untouched by alcohol. The mucin here is both intracellular and free in the tissue and differs in no way from that in tissue treated with alcohol.

It can be clearly shown that mucin arises in oligodendroglia cells undergoing the regressive change called acute swelling, but which should strictly be called "mucoid degeneration." We have never seen such degeneration in any other type of glia cell, and final proof that the oligodendroglia alone are concerned in its production is our ability to find it in the cytoplasm in tumors reported by Bailey and Bucy<sup>13</sup> to be composed of these cells only, the oligodendrogliomas.

The liberation of the mucin by the degenerating cells, which tend to clump normally, and the coalescing of the globules of mucin form the large grapelike bodies. This substance tends to move toward the blood vessels, along which it is probably carried to the subarachnoid space.

We have used the term mucin rather freely and feel our justification only in the fact that it stains as mucin by so-called mucin stains. The inadequacy of histochemical means of differentiation is well known, yet until more accurate means are at our disposal, we must designate these substances staining with mucicarmine as mucin. The disposal of the mucin, once it is formed, can easily be followed from the degenerating oligodendroglia cell to vascular and subarachnoid spaces, but the mechanism of its intracellular formation is totally unknown.

#### SUMMARY

Mucoid degeneration and acute swelling of the oligodendroglia represent the same process, which is a specific type of regressive change found in no other glia form. It is not found in normal brains.

The mucin is not formed by degeneration of myelin sheaths or ganglion cells nor is it phagocytosed by the oligodendroglia. It is not artefact, but a product of the oligodendroglia themselves. Alcohol is not a necessary "sensitizer" to bring out the mucin, as ordinary frozen sections stained with mucicarmine reveal the mucin.

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13. Bailey, P., and Bucy, P. C.: Tumors of the Brain Composed of Oligodendroglia, *J. Path. & Bact.*, to be published.

Mucocytes form free in the nervous tissue by the liberation of intracellular mucin and its coalescing into grapelike bodies. The mucin eventually reaches the perivascular spaces by which route it is probably conveyed to the subarachnoid space.

The mucin frequently drops out of the tissue and cells, resulting in tissue spaces that are unstainable. This mucin is recoverable from the bottom of the specimen container.

# PRENATAL VOLVULUS OF SMALL AND LARGE INTESTINE CAUSED BY A MESENTERIC CYST\*

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Cases of mesenteric cyst have been presented from time to time in detail because of the obscurity of their origin and the difficulty of their diagnosis. A wide difference of opinion exists as to their genesis, and a positive diagnosis has probably never been made prior to autopsy or operation. Until lately their significance has not been fully appreciated. Their history has been divided into four periods. The first, from 1507 to 1850, the period of postmortem observations, dates from the first description of a case by the Florentine pathologist Benivieni. The second, from 1850 to 1880, was marked by the occasional accidental finding of one of these cysts at operation, from which no recoveries are reported. During the third period, from 1880 to 1900, there were some cases of recovery after operation in which the cyst had been accidentally found. The fourth and present period, since 1900, has been marked by occasions when the condition has been suspected and a tentative diagnosis made before operation. In our case, no diagnosis of the existing condition was made before death.

## REPORT OF CASE

*History.*—On Aug. 14, 1928, at 10:35 p. m., a female colored child, weighing 7 pounds, 7 ounces (3.7 Kg.) was delivered without difficulty. The infant presented no external abnormalities, and cried lustily. Following its first feeding, however, it vomited greenish fluid. It immediately began to pursue a downward course with vomiting after every feeding. Two days after delivery, the infant no longer fed well, and its skin became cold and clammy. On the third day, bottle feeding was tried, but without benefit. On the fifth day post partum, it vomited a dark-colored fluid. Soon after this jaundice appeared, and the infant died in the evening. The temperature was always between 97 and 98.8 F., but the weight had come down from 7 pounds and 7 ounces (3.7 Kg.) to 6 pounds and 5 ounces (2.6 Kg.). The blood count was as follows: red cells, 3,200,000; hemoglobin, 55 per cent; color index, 0.86; white cells, 21,800; polymorphonuclear neutrophils, 40 per cent; lymphocytes, 45 per cent, and large mononuclears, 15 per cent. The bleeding time was one-half minute and the coagulation time three minutes.

*Autopsy.*—The autopsy was performed the morning after death. Rigor mortis was complete. The body was emaciated. The fontanels were open and the cranial sutures loose, but there was no craniotabes. The skin, mucous membranes and conjunctivae were jaundiced. The chest was symmetrical. The pleural cavities

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\* Submitted for publication, May 18, 1929.

\* From the Pathologic Laboratory, Harlem Hospital.

contained no free fluid. The lungs were voluminous and hypercrepitant. The visceral pleura was salmon pink, but on section the lungs were moist and dark purplish red. The blood vessels and bronchi were normal. The heart was normal in size, shape and position. The valves were normal; the foramen ovale and the ductus arteriosus were patent. The abdomen was slightly distended, but contained no free fluid. The liver was of usual size but of a dark greenish color. The gallbladder and bile ducts were normal. The spleen was small and firm, and on section the malpighian bodies were visible. The pancreas and the suprarenal glands presented no abnormalities. The kidneys were of usual size; their capsules



Fig. 1.—A “mesenteric” cyst dating from before the fourth month of prenatal life, and causing a volvulus of the small and the large intestine.

stripped easily, disclosing greenish, congested surfaces; several uric acid infarcts were visible. The renal pelves, ureters and bladder were normal.

In the mesentery of the lower jejunum was a large oval cyst, which measured 8 cm. in its longest diameter and was firm. A loop of jejunum lay across its anterior surface and was apparently closely related to it. The jejunum here seemed flattened by pressure of the underlying tumor. Just above the tumor, the small and the large intestine had been involved simultaneously, as illustrated in figure 1, in a volvulus four and one-half turns in a clockwise direction. The

portion of the intestine lying proximal to this was dilated to a diameter of 3.5 cm., while the distal portion measured only 8 mm. in diameter. The cyst and the volvulus were found in the umbilical region of the abdomen. There was no loop of large intestine present on the right side. Although the large intestine was undescended and unrotated, the cecum was not quite of the infantile form. The appendix arose well to the left of its base.

The uterus was small and infantile, three fifths of it consisting of cervix. The rugae were hypertrophied and extended into the corpus. The external os was patent and measured 1 cm. in diameter. The lower third of the cervix dipped into the vagina. The adnexa were normal.

*Diagnosis.*—Mesenteric cyst, causing prenatal volvulus of the small and the large intestine, with obstruction of the jejunum above the volvulus; undescended large intestine; icterus of viscera, skin and mucous membranes, bilateral lobular pneumonia; patent foramen ovale and ductus arteriosus; uric acid infarcts of the kidneys.

*Microscopic Examination.*—On section of the cyst, after it was fixed, it was found to contain a slightly cloudy yellowish fluid, which flowed freely. The inner wall of the cyst felt velvety, and that portion of its dome adjacent to the underlying intestine appeared to be continuous with the intestine. Microscopically, the cyst wall consisted of four coats, mucosa, submucosa, two layers of muscularis and a serosa, exactly as in the intestinal canal proper. Throughout the circumference, the inner circular and the outer longitudinal layers of smooth muscle were distinctly demarcated and well developed, being arranged at right angles to each other as in the adjacent intestine. At the junction of cyst and bowel, however, the inner circular layer of the cyst divided into two portions which encircled the intestine and formed the latter's inner circular layer. The layer of muscle between intestine and cyst was common to both; the wall at this point from the lumen of the cyst to the intestinal lumen consisted of mucosa of cyst, submucosa, circular muscle, submucosa and mucosa of intestine. The external longitudinal muscle layer was common to both cyst and intestine. The mucosa of the intestine adjacent to the cyst was somewhat altered by pressure of the cyst. The villi were flattened and, microscopically, the mucosa was changed abruptly. Over this area, the mucosa was flattened and the glands were reduced in number; here the high columnar cells were more cuboidal and the nuclei more uniformly circular and crowded. The mucosa of the cyst was exactly similar to the mucosa of the flattened base of the adjacent intestine just described, except at the common septum, where it was much thinner than elsewhere and for short distances even appeared to be flattened completely. Apparently, the pressure from the overdistended cyst acting on the septum between the lumen of the bowel and that of the cyst, which was naturally its weakest point because of the absence of a portion of the muscular envelope present elsewhere, accounts satisfactorily for the stretching of the septum producing the change in the cyst and the bowel just described (fig. 2).

#### COMMENT

Two cases of prenatal volvulus due to so-called mesenteric cyst have been described in the literature in the past fifteen years. In these cases, the volvulus involved only the small intestine, and operative procedure was resorted to in both, but without success. These cases have been referred to as rare, if not unique. Our case may be considered still more unusual in that an undescended large intestine, together with the

small intestine, was involved in the volvulus. The microscopic observations already mentioned, moreover, may serve to clear up the problem of etiology and point out a fallacy in the surgical treatment.

Moynihan's<sup>1</sup> classification (1897) of cysts is probably the first comprehensive one, namely: (1) serous, (2) chylous, (3) hydatid, (4) blood, (5) dermoid and (6) cystic malignant disease. Only one group in this list suggests an embryonic origin.

In 1900, Dowd,<sup>2</sup> in discussing a case of multilocular cystadenoma of the transverse mesocolon, resembling a cystadenoma of the ovary, suggested its probable origin as an embryonic ovarian sequestration and proposed this classification: (1) embryonic cysts, (2) hydatid cysts and (3) cystic malignant disease. In doing so, he also suggested that chylous, sanguineous and serous cysts are merely the result of effusion of these characteristic fluids into preformed cysts, and he made the

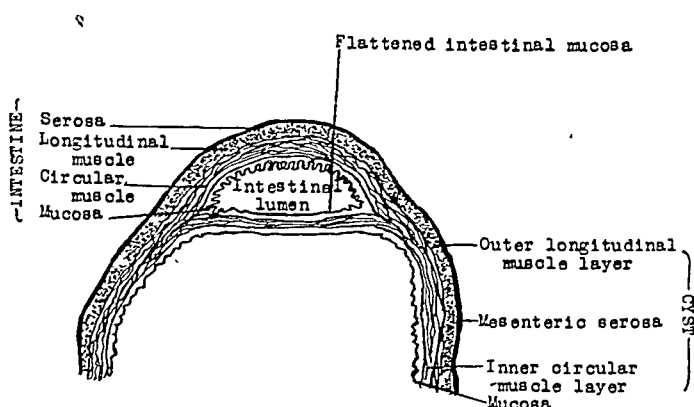


Fig. 2.—Diagram of a transverse section through the "mesenteric" cyst of figure 1. It shows the cyst invaginated between leaves of the mesentery of the small intestine.

statement that cysts that have the structure of the intestinal wall suggest sequestration from the intestine. This statement is interesting in view of our observations and those of others.

To this last classification, Ayer, in 1906, added: (4) cysts arising from glandular structure of the intestinal wall and (5) cysts of the normally retroperitoneal organs. However, group 4 is at best only a subdivision of Dowd's group 1, and group 5 does not, by its very definition, comprise mesenteric cysts.

Noisi,<sup>3</sup> in 1907, further subdivided Dowd's group 1 into (a) cysts formed by sequestration from the bowel during development and (b) cysts formed from Meckel's diverticulum when it arises from the concave side of the bowel. To Dowd's group 3, he added cysts arising from

1. Moynihan: *Ann. Surg.* **26**:1, 1897.

2. Dowd, C. N.: *Ann. Surg.* **32**:515, 1900.

3. Noisi, F.: *Virchows Arch. f. path. Anat.* **190**:217, 1907.

retroperitoneal organs, namely, germinal epithelium, ovary, wolffian body and müllerian duct. He considered half of all mesenteric cysts as acquired and placed so-called lymphatic and chylous cysts in this group.

In 1924, Carter<sup>4</sup> proposed another modification of Dowd's classification, as follows: (1) true mesenteric cysts (embryocystomas, enterocystomas, obstructive), (2) dermoid cysts, (3) cystic malignant disease and (4) parasitic cysts.

Higgins and Lloyd,<sup>5</sup> in 1924, proposed this other classification: (1) those of embryonic origin arising from mesodermal remnants incarcerated behind the developing peritoneum and subsequently migrating forward between its layers; (2) those of intestinal origin arising from the bowel during development as diverticula or possibly at times derived from the persistent portion of the vitelline duct.

Aschner<sup>6</sup> (1924), reviewing twenty different cases from the literature, concluded that the enterocystomas described by most writers were due to faulty involution of the omphalomesenteric duct, but, in his opinion, conclusive proof of this theory must await further observations.

#### CONCLUSIONS

The idea that a portion of an embryonic tissue or organ may become sequestered and still continue to develop is not new. A group of epithelial cells with its own connective tissue support may become more or less independent for its growth and develop as a cyst the lumen of which is constantly enlarged by the retention of its own secretion and desquamated epithelium. Miller<sup>7</sup> quoted Lewis and Thiyng as finding a "regular occurrence of intestinal diverticula in embryos of pig, rabbit and man." However, he arrived at the general agreement that most juxta-intestinal cysts, even when intramesenteric, have their origin in the vitelline duct or Meckel's diverticulum, and was of the opinion that variation in the location of the diverticulum is marked. Hennig<sup>8</sup> suggested that shrinkage of the mesentery of a laterally placed diverticulum might pull it down into the mesentery. Both of the types mentioned would naturally resemble the adjacent bowel remarkably. The gross and microscopic appearance of Miller's case and our own rather definitely place both of them in the group of mesenteric cysts arising from sequestration. It will be noted that in both instances the inner circular layer of muscle was common to both cyst and bowel. If the cyst had been the result of remnants of omphalomesenteric duct, there

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4. Carter, R. A.: *Surg. Gynec. Obst.* **33**:544, 1921.

5. Higgins, T. T., and Lloyd, E. L.: *Brit. J. Surg.* **12**:95 (July) 1924.

6. Aschner, P. W.: Enterocyst of Ileum, Causing Obstruction, *Arch. Surg.* **9**:226 (July) 1924.

7. Miller, R. T.: *Bull. Johns Hopkins Hosp.* **24**:316, 1913.

8. Hennig: *Zentralbl. f. Gynäk.* **4**:398, 1880.

would have been no necessity for such a close relationship. Both the structure and the arrangement of these cysts point to an enterogenous origin by a process of sequestration during embryonic life. We may therefore state that we are dealing with a cyst at the base of the intestine extending into the mesentery and separating its leaves, and not with a true mesenteric cyst, as it is commonly called. This terminology may be considered similar to that used in calling the extension of a uterine fibroid into the broad ligament a "fibroid of the broad ligament."

The onset of the cystic growth in our case may be definitely dated from before the fourth month of embryonic life, because after the fourth month the portion of the intestine forming the cecum rotates downward to the right side, and in our case an undescended cecum was contained in the volvulus. It therefore follows that the cyst must have been large enough to interfere with the normal development of the cecum at or probably before the fourth month of gestation.

To bear out further the probability that most, if not all, mesenteric cysts with an enterogenous histology are not due to growth of remnants of the vitelline duct, we can add the evidence of such reported cases as those in which the cysts were present in the wall of the intestine and in the lumen of the intestine, as well as those in which they were far removed from the usual site of Meckel's diverticulum, e.g., high up in the duodenum or at the ileocecal valve. Such cysts in the lumen of the intestine have been called enterocysts to differentiate them from mesenteric cysts. One, however, is just as much of a misnomer as the other, for what we actually have is three types of enterogenous cysts: (1) cysts in the wall of the intestine, (2) cysts extending into the mesentery and (3) cysts extending into the lumen of the intestine. As implied before, this classification is entirely analogous to the classification of uterine fibroids into intramural, subserous and submucous. Recent articles on this subject have, by their evidence, all tended toward a similar conclusion, and we feel that our report and suggestions deriving from this case help a good deal toward the definite establishment of the nomenclature proposed.

The importance of accepting this nomenclature as reflecting the actual pathologic condition is well illustrated in previous reports of the surgical difficulties encountered in cases of so-called mesenteric cysts. The following résumé of a recent article<sup>9</sup> serves well to illustrate our point:

A girl, aged 3, was admitted to the hospital with a history of periodic attacks of abdominal pain and vomiting since birth. Her abdomen was big and never varied in size. An exploratory operation was performed two days after admission. When the abdomen was opened, a lobulated cyst, the size of a small football, was found attached to the mesentery of the small bowel, about 45 cm. from the ileo-

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9. Wade, R. B., and Steigrad, J.: *M. J. Australia* **15**:465, 1928.



cecal junction. The small bowel appeared to curve in and around the cyst, *making separation very difficult* (italics ours). Therefore, about 25 cm. of small intestine was resected with the cyst. The patient made an uneventful recovery. The microscopic report suggests that the wall of the cyst and the septum between loculi showed a lymphangiomatous structure with conspicuous blood vessels and strands of involuntary muscle in the connective tissue. No epithelial structures were seen. It was called a cyst of lymphatic origin.

We believe this cyst to have been a greatly dilated enterogenous cyst extending into the mesentery. The enormous distention probably caused a complete flattening of the mucosa of the cyst, such as was caused to some degree in our case, and rupture of the muscle wall of the cyst caused its lobulated appearance. It will be noted that an attempt was made at separation of the cyst from the intestine. This same procedure has been attempted in the other cases reported, without success; a resection was necessary in all. As a matter of fact, because of the pathology with special reference to the histology of the cyst and intestine, a separation should not be attempted, but resection should be undertaken at once. The length of the procedure would thus be lessened and useless and harmful manipulation of the viscera be avoided.

#### SUMMARY

A case of prenatal volvulus of the small and the large intestine in a full-term female colored child with an undescended large intestine was caused by a mesenteric cyst. The cyst was microscopically enterogenous and contiguous with the overlying intestine. It had a mucosa, an inner circular layer and an outer longitudinal layer of smooth muscle and a serosa. The inner circular layer of the cyst split to encircle the adjacent intestine at the junction of the cyst and the intestine, and the outer longitudinal layer was common to both.

Classification of cysts has changed materially from Moynihan's purely descriptive one to the more recent attempts at an etiologic nomenclature. The histologic structure of juxta-intestinal mesenteric cysts has given rise to the idea of their origin from vitelline duct remnants. Against this theory is the fact that these cysts have been found from duodenum to cecum. Lewis and Thyng found a regular occurrence of intestinal diverticula in embryos of pig, rabbit and man. Therefore, these cysts are probably enterogenous in origin, and since they are found in the wall of the intestine, extending into the mesentery, and extending into the lumen of the intestine, we may consider them to be analogous to the intramural, subserous and submucous fibroids of the uterus.

The cyst caused the volvulus before the fourth month of intra-uterine life, as shown by the presence of an undescended cecum in the volvulus.

As a result of the histologic observations, we believe that in these cases separation of the cyst from the intestine should not be attempted, but a resection should be undertaken at once.

# IRREGULARITY IN THE ESTRUAL CYCLE OF THE WHITE RAT FOLLOWING OPERATION ON THE OVARIES \*

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It was because of a vital clinical interest in the functional menstrual irregularities in young women and in the hope of gaining some information as to the physiology of menstruation and estrum that this study was attempted. Whether estrum and menstruation represent related and similar phenomena is still a debated question, but there is no reason to suppose that in the essentials they are different. The recurring estrual period of the smaller animals and the menstrual period in the higher animals and that of human beings consist of two phases: one during which the uterus is preparing for the reception of the ovum, and one when the unfertilized ovum, together with the endometrium, are degenerating in preparation for another period. In the animal, the external evidence of this recurring phenomenon is the peculiar sexual behavior of the female and the acceptance of the male. This gave origin to the name estrum or rutting period. It occurs during the preparatory or upbuilding phase. In the higher animals and in the human being, the external evidence of the cyclic phenomenon, the discharge of blood, occurs during the degenerating phase and is called menstruation.

One conspicuous feature of most of the cases of true functional irregularity in young women is an interruption of the usual rhythm of the menstrual cycle. This usually begins to be evident soon after the onset of menstruation. There are long or short periods of menstrual bleeding with varying intervals between. At times, there seems to be an attempt to establish a rhythm; for a few months the periods may become almost regular and normal; then suddenly the rhythm becomes entirely disturbed. In some cases, the long periods of vaginal bleeding are more conspicuous than the long periods of amenorrhea. I have accordingly tried to classify the cases into two groups:<sup>1</sup> those of the metrorrhagic type and those of the amenorrheic type of ovarian dysfunction. A person may revert from one type to the other.

It has been noted clinically that after an operation on the ovaries of a younger woman with resection of a large portion of each ovary,

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\* Submitted for publication, March 26, 1929.

\* From the Division of Medicine of The Mayo Clinic.

1. Drips, Della C., and Ford, Frances A.: Irradiation of Ovaries and Hypophysis in Disturbances of Menstruation, J. A. M. A. **91**:1358 (Nov. 3) 1928.

leaving only a small bit of functioning tissue, or after a severe pelvic infection involving the ovaries, often an irregularity of menstruation develops which simulates functional irregularity. That is, an absolute lack of rhythm develops, so that short or long periods of vaginal bleeding, sometimes difficult to check, may follow short or long periods of amenorrhea.

Often, in both the truly functional and the postoperative or post-infection type of irregularity, by substituting ovarian products it is possible to bring about a simulation of regularity; it has seemed, therefore, that in all these groups there is a deficiency of certain ovarian hormones. Just what factor is necessary for the establishment and continuation of the menstrual rhythm is not, as yet, known.

At operation, in cases of ovarian dysfunction, it has been noted that large cystic ovaries were present, or ovaries filled with cystic follicles; what has been described as a sclerotic capsule may be encountered, and the theory has been that the rhythm has been disturbed because of the inability of the follicles to rupture. Therefore, it would seem that the ovaries remain in one phase of the cycle and the endometrium remains in the corresponding hypertrophic phase, and hence the continued bleeding. Operations on the ovaries, such as stripping off the capsules, puncturing the cystic follicles or resecting portions of them, may bring back the rhythm to the cycle, but often only temporarily.

Believing, then, either that inability of the follicles to rupture or that an insufficient amount of functioning ovarian tissue or both might explain the interruption of the rhythm, an attempt has been made to produce a similar irregularity or lack of rhythm in the white rat. Plastic operations were performed on the ovaries which it was believed would either stop the rupturing of the follicles or reduce the ovarian tissue to a minimum. Then, if arrhythmia was established, it was hoped an insight might be obtained into the mechanism of estrum by a study of the attendant ovarian pathologic changes.

The white rat was chosen because the estrual cycle in this animal had been exhaustively studied by Long and Evans<sup>2</sup> and the various stages of the estrual period as evidenced by vaginal smears were known. Also, the white rat stands operation well, and is resistant to disease.

In order that I might become familiar with the normal estrual cycle in the rat and its associated phenomena, a long time was spent studying the cycles. One hundred and twenty-five female rats were observed for periods varying from four weeks to one and a half years. The date of birth, the date of the opening of the vagina and the date of the first estrum were known in many instances. All the rats were kept from males, since coitus, as has been noted by Long and Evans, always

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2. Long, J. A., and Evans, H. M.: *The Oestrous Cycle in the Rat and Its Associated Phenomena*, Memoirs University of California, 1922.

lengthens the interval between estrual periods. Daily vaginal smears were made for all rats. The typical cornified smear occurred every fourth day. This smear was readily detected grossly because the cheesy material could be easily seen on a glass slide. It was the external evidence of an estrual period.

The smears were best taken at the same time each day, because a few hours' difference sometimes made it seem as if there had been a day more or less between the periods of cornification. Any one who has observed many rats for a long time cannot help being forcibly impressed with the regularity of the cycle. I wish to emphasize this, since from certain available literature it would seem that the cycle was subject to variation due to changes in rations and in living conditions. The rats had the same rations as the other rats in the laboratory: oats, prepared animal biscuits and bread and milk every few days. The number in each cage was limited to five. The rats were of a hardy strain, a mixture of wild and laboratory strains. There were a few litters that seemed to tend to some irregularity, but, in general, the regularity was as predominant as is regularity of menstruation among women. Ordinary illnesses, such as respiratory infections and diseases of the ear, which are common among rats and often severe, apparently had little effect on the regularity of the cycle.

In a few rats with diarrhea and considerable emaciation, the cycles stopped. This usually occurred as soon as emaciation was evident. Only fourteen of the rats died of intercurrent infection, so there was not much opportunity of observing the effect of disease on the cycle. Marked irregularities of the cycle, such as short or long-continued periods of cornification with varying intervals between, were found at necropsy to have occurred in rats with marked pelvic infections, pus being present in the cornua and adhesions being found about the ovaries. These observations were interesting in view of the experimental work. It has been difficult to determine how long the ovarian activity continues in the rat. Rats born in the laboratory were still having regular periods at the age of 19 months. After this, the periods seemed to become more irregular. The average length of life is about 2 years. The vagina opened at seventy days, on the average, and the first estrum occurred at seventy-eight days, on the average. There was some irregularity of the cycle for the first two months. This consisted in longer intervals, usually a multiple of four days between periods of cornification, so that for experimental purposes it was best to use rats about 6 months of age. Estrum was not observed during pregnancy; it was noted several times during lactation. It was possible at times to miss the typical cornified or estrual smear grossly, so that to be absolutely sure of the stage of estrum in vital experiments one had to fix the slides and stain them with hematoxylin and eosin.

My primary interest, as stated, was to try to produce irregularities in the cycle of the rat which might add something to the knowledge of the physiology of the ovaries, and to the understanding of why these irregularities occur in human beings. Healthy female rats, aged about 6 months, were observed for a sufficient period to know they were having normal cycles, and then operations were performed on the ovaries with a view either to stopping the rupture of the follicles or to reducing the healthy ovarian tissue to a minimum or both.

#### EXPERIMENTAL PROCEDURES

In the first series of rats, both ovaries were exposed and pure carbolic acid was applied to the surface of each, either with the periovarian membrane intact or after it had been stripped. In the second series, one ovary was completely removed and the remaining ovary treated, as in the foregoing procedure. In the third series, a fine needle was run many times through both ovaries in an attempt to rupture all the follicles present and to produce a reaction throughout the ovary. In a few cases, one ovary was removed and the remaining one was needled.

Twenty-eight animals, in all, were operated on. These operations were all done under ether anesthesia and with the most careful aseptic precautions. By the application of carbolic acid to the surface of the ovaries, it was hoped both to reduce the amount of functioning ovarian tissue and to cause enough fibrous adhesions about the ovary to prevent the follicles from rupturing. After the operation, daily vaginal smears were taken and the cycles observed for a long period. A litter mate was kept as a control for comparison of the cycles. It was soon found that the opening of the abdomen and the anesthetic had no effect on the regularity of the cycle, so that the controls were not subjected to this procedure. Finally the rats were killed, the uterus and ovaries were observed grossly and the organs were fixed in Zenker's solution and embedded in paraffin and studied microscopically. Complete serial sections were made of the ovaries. Only one animal died immediately after operation. This rat should not have been included in the series, as it had had a severe respiratory infection, but it had seemed to recover from this and regular cycles were occurring. Some ascites was noted in the abdomen at the time of operation (tables 1 to 3).

#### RESULTS

*Series 1.*—There were eleven animals in the first series. In these, both ovaries were treated with carbolic acid with or without stripping off the periovarian membrane. In only three of the animals did any irregularity follow immediately after the operation and continue to death. This was due beyond a doubt to the marked acute reaction to the carbolic acid for at necropsy dense adhesions indicative of severe peritonitis were present all through the pelvis. In these three animals, a respiratory infection with diarrhea developed, and the animals died or were killed within seventy-eight days after operation. Two were in estrum when killed. The ovaries contained some normal follicles and corpora lutea, and there was evidence of the severe inflammatory reaction. In another animal, irregularity developed after two normal

cycles. This consisted of prolonged periods of cornification with longer intervals between, so that the normal rhythm was decidedly disturbed. Finally, a period did not occur for twenty-eight days. At

TABLE 1.—*Results of Experiments in Which Both Ovaries Were Carbolized (Series 1)*

Rat	Irregularity of Estrual Cycle		Days After Operation Before Death	Character of Smear on Day of Death	Structures in Ovaries
	Appearance After Operation, Days	Character			
1*	80	Periods of cornified cells lasting from three to four days; two long intervals	240	Diestrum; no estrum for forty-five days before death	Left ovary: five old corpora lutea and two or three small follicles. Right ovary: five large cysts, four old corpora lutea, no normal follicles
2*	75	Periods of cornified cells lasting from three to four days; two long intervals	240	Dry; epithelial cells only; first stage (Long and Evans)	Few normal mature follicles and early corpora lutea; several follicular cysts
3†	105	Longer intervals between periods; two prolonged periods of cornification	240	Estrum	Few normal structures; right ovary could not be distinguished grossly; microscopic sections not made
4	105	Longer intervals between periods	240	Estrum	Right ovary could not be detected grossly; microscopic sections not made
5	193	Irregular periods with a tendency to prolongation of cornification	193	Diestrum; no estrum for sixty-eight days before death	Left ovary: only corpora lutea (three appeared to be early). Right ovary: few normal follicles and corpora lutea
6	Immediate	Only two estrual periods on the tenth and sixteenth days	38	Diestrum; no estrum for twenty-two days before death	Few apparently normal structures present; much evidence of inflammatory reaction; ovarian tissue infiltrated with lymphocytes
7	Immediate	Three estrual periods at varying intervals	45	Estrum	About the same as in rat 6; normal structures were present but much inflammatory reaction
8	Immediate	No estrum for thirty-eight days; then fair regularity to death	76	Estrum	Normal structures; marked reaction
9	...	After two cycles, prolongation of periods of cornification with longer intervals between	78	Diestrum; no estrum for twenty-eight days before death	Few fairly normal follicles and corpora lutea; both ovaries so small that they could not be identified grossly
10	80	Prolongation of intervals between periods	180	Diestrum; last estrum two days before death	No large or mature follicles in either ovary; few small but apparently healthy corpora lutea (not early)
11	32	After eight cycles one prolonged period of cornification; irregular intervals between	335	Diestrum; last estrum thirty days before death	Left ovary: several mature follicles and several early corpora lutea. Right ovary: two normal mature follicles and two large corpora lutea (not definitely early)

\* Ovaries carbolized after periovarian membrane was stripped off both ovaries.

† Ovaries carbolized after periovarian membrane was stripped off right ovary.

necropsy, the left ovary was found to be extremely small and was embedded in a mass of adhesions; it was not possible to be sure grossly of the right ovary. Microscopically, what was left of each ovary contained a few fairly normal appearing follicles and corpora lutea.

The remaining seven animals did not manifest any immediate post-operative irregularity but continued to have normal, regular cycles from 75 to 105 days after operation, after which each developed some irregularity. In at least five, a definite lack of rhythm was present to

TABLE 2.—*Results of Experiments in Which One Ovary Was Removed and the Other Carbolized (Series 2)*

Rat	Irregularity of Estrual Cycle		Days After Operation Before Death	Character of Smear on Day of Death	Structures in Ovaries
	Appearance After Operation, Days	Character			
1	Immediate	Long and short periods of cornification with long and short intervals between	130	Diestrum; last estrum twenty-three days before death	Five old corpora lutea, one cystic corpus luteum, one small follicle, one degenerating follicle; ovary so small that it could not be detected grossly
2	115	Slightly longer intervals between estrums	210	Estrum	Six or seven old corpora lutea, three follicles changing into corpora lutea without rupturing; no other follicles
3	...	After two estrual periods, prolonged periods of cornification first and later occasional skipping of a period	240	Epithelial cells only; first stage (Long and Evans)	No microscopic sections made; ovary lost in embedding; grossly, it was size of a pinpoint
4	Immediate	Increased intervals between periods; slight prolongation of a few periods of cornification	180	Diestrum; last estrum fifteen days before death	No microscopic sections made; ovary lost in process of embedding; grossly, left ovary was buried in mass of adhesions to lower pole of kidney
5	Immediate	One prolonged period of cornified cells; long intervals	73	Diestrum; last estrum occurred twenty-five days before death	No healthy mature follicles or early corpora lutea
6	Immediate	Periods of cornified cells slightly prolonged; slightly irregular intervals between	530	Estrum	Healthy follicles of medium size, two normal mature follicles, many corpora lutea of various ages, definitely early (?)
7	...	Estrual cycle regular	395	Dry but not cornified; first stage	Three follicles, which appeared healthy; nine degenerating corpora lutea, early (?)
8	...	Estrual cycle regular except for one period of three and one of four days of cornified cells	395	Estrum	Eight corpora lutea of various ages; two corpora lutea cysts, two mature follicles
9	40	Skipped periods, but rhythm seemed to be maintained	395	Late estral smear (moist)	Eight corpora lutea, a few of which appeared early; five mature follicles
10	16	After four cycles, occasional prolonged periods of cornification with varying intervals between	395	Diestrum; last estrum five days before death	Mass of follicles, no corpora lutea, three transformed follicles with ova still present
11	53	Some periods skipped; after the tenth month daily cornified smears for twenty-five days	369	Purulent; last cornified smear occurred six days before death	Severe pelvic and abdominal infection, abscesses; impossible to identify the ovary

the day of death. The pathologic change in all these ovaries was marked. The amount of ovarian tissue had been greatly reduced, the ovaries being so small at times that they could not be detected grossly. However, microscopically, a few large or mature follicles and corpora lutea were present in the ovaries of all but two rats (figs. 1 to 4).

Rat 1 did not have an estrum for forty-five days before death, but the smear of rat 10 was positive two days before death. In both these animals, the irregularity began eighty days after-operation and continued to death. The cycle was entirely without rhythm in rat 1.

*Series 2.*—In the second series, there were eleven animals in which one ovary was removed and the other ovary carbolized. It was hoped that by removing one ovary the amount of functioning ovarian tissue might be reduced still more. In four of these animals, the cycle became irregular immediately after operation. Experience with the first series seemed to show that the reaction to the carbolic acid had perhaps been

TABLE 3.—*Results of Experiments in Which Both Ovaries Were Needed (Series 3)*

Rat	Irregularity of Estrual Cycle		Days After Operation Before Death	Character of Smear on Day of Death	Structures in Ovaries
	Appearance After Operation, Days	Character			
1	30	Prolonged periods of cornification with varying intervals between	165	Diestrums; last estrum ten days before death	Right ovary: normal structures present; increase in fibrous tissue; left ovary could not be identified
2	Immediate	A long interval without periods (diarrhea a factor?)	120	Diestrums; estrum two days before death	A few normal structures in both ovaries; the amount of ovarian tissue was greatly reduced
3*	64	After sixteen cycles, several periods of cornification lasting several days; however, rhythm appeared to be maintained; late long intervals between periods	140	Bloody vaginal smear; fairly recent blood clot in left cornu; last estrum occurred fifteen days before death	Normal structures present
4†	Immediate	Periods of cornification at very irregular intervals	129	Estrum	No microscopic sections made; the ovarian tissue was greatly reduced grossly

\* Right ovary entirely removed.

† Left ovary entirely removed.

more marked in these rats, but they all survived this initial period of reaction and were observed for a considerable period; some irregularity continued in all, and was marked in rats 1 and 5. These two had a complete lack of rhythm after operation and the estrual periods seemed to cease entirely, in rat 1, 117 days after operation and in rat 5, 48 days after operation. The animals were killed 130 and 78 days, respectively, after operation, and healthy mature follicles or early corpora lutea were not present in the remaining ovary of either. The remaining ovary of rat 1 was so small that it could not be detected grossly; it was found by cutting serial sections of tissue from the ovarian region (fig. 5). Certainly, in these two animals, a complete lack of estrual rhythm simulating the postoperative irregularities in young women had been produced by reducing the ovarian tissue to a minimum.



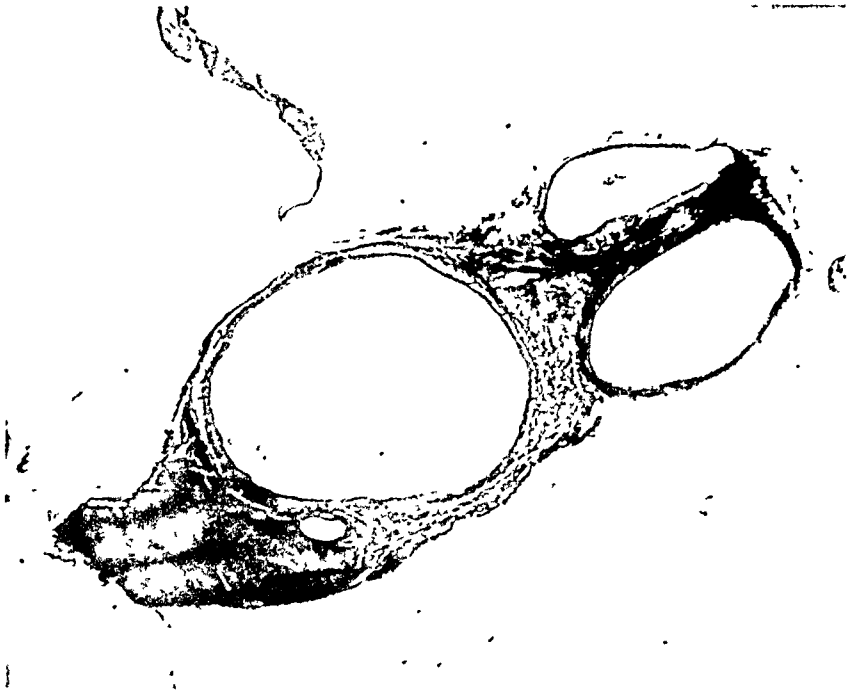


Fig. 1 (rat 1, series 1).—Cross-section through the right ovary of a rat in which both ovaries had been carbolized after the periovarian membrane was stripped off. The ovary shown contained five large cysts and four old corpora lutea. Normal follicles were not present.



Fig. 2 (rat 1, series 1).—Cross-section through the left ovary of a rat in which both ovaries had been carbolized after the periovarian membrane was stripped off. There were five corpora lutea, none of which appeared to be an early structure, and three very small follicles.



Fig. 3 (rat 10, series 1).—Cross-section through the left ovary of a rat in which both ovaries had been carbolized. This ovary could not be detected grossly. It was found by serial sections. It contained three corpora lutea. Follicles were not present.



Fig. 4 (rat 10, series 1).—Cross-section through the right ovary of a rat in which both ovaries had been carbolized. There were present several corpora lutea, two cysts and many atretic follicles. Healthy follicles were not present.

The estrual cycle in rat 3 became irregular after two estrual cycles, and sometimes rhythm was entirely lacking. After 240 days, the animal was killed in estrum. There was present grossly a tiny bit of ovarian tissue on the right, too small to measure. It resembled a cyst about the size of a pinpoint. It was lost in the process of embedding. The estrual cycle in rat 2 became irregular after 115 days. This animal was killed 240 days after operation during estrum. The ovary contained seven old corpora lutea and three follicles changing into corpora lutea without rupturing.

Three animals of the second series maintained more regular periods than any of the animals operated on. They were all observed for



Fig. 5 (rat 1, series 2).—Cross-section through the remaining ovary of a rat in which the other ovary had been removed and the remaining one carbolized. The ovary was surrounded by organs from which it could not be separated. It contained five small corpora lutea and one fairly healthy follicle.

thirteen months and all were in a stage of estrum when killed. These in their single remaining ovaries showed the largest number of normal follicles and corpora lutea of any of the animals operated on.

In rat 10, after four regular, normal cycles, the cycles became irregular; definite rhythm was not maintained; occasional prolonged periods of cornified cells with varying intervals between occurred to the day it was killed, thirteen months after operation. The last estrum occurred five days before death. The remaining ovary was made up of a mass of follicles. Corpora lutea were not present. These follicles

were being transformed into corpora lutea without rupture, the ova being still present in the structures (fig. 6).

In rat 11, a late pelvic infection apparently completely upset the rhythm; a prolonged period of cornification lasting twenty-five days occurred shortly before death.

*Series 3.*—In the third series, in which both the ovaries were needled or one was removed and the other needled, success in reducing the amount of functioning tissue or in preventing the follicles from rupturing

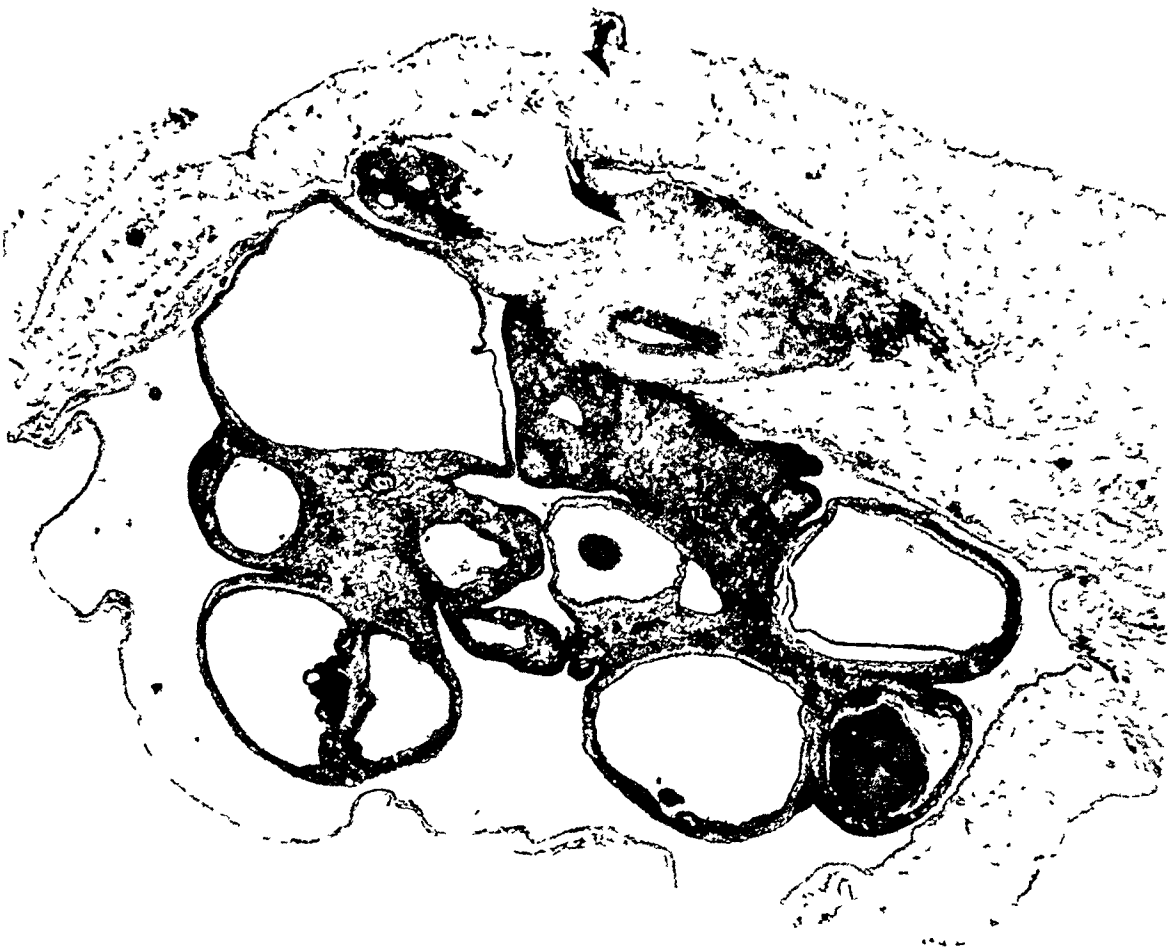


Fig. 6 (rat 10, series 2).—Cross-section through the remaining right ovary of a rat in which the left ovary had been removed and this one carbolized. It is shown surrounded by the distended periovarian membrane, filled with fluid. The ovary itself was a mass of follicles and follicular cysts. Corpora lutea were not present

was not so complete. An irregularity of the cycle developed in each case, however, and in two cases the irregularity came directly after operation and continued. In two animals (rats 1 and 4), the cycle was entirely without rhythm. The cycle in rat 1 did not become irregular until thirty days after operation, but thereafter prolonged periods of cornification continued to occur with varying intervals between them

until the animal was killed 165 days after operation. The left ovary could not be identified. The right ovary contained a few normal structures. There was a marked increase in fibrous tissue. The cycle in rat 4 became irregular following operation and continued so, the cycle being entirely without rhythm. The animal was killed in estrum, 129 days after operation. The left ovary was very small and was lost.

Naturally, it was difficult to gage just how much destruction of tissue occurs as a result of experimental trauma to the ovaries. As it happened, in the second series of rats each of which had had one ovary entirely removed, there were three rats that had more healthy structures in their remaining ovaries than any animals of the first series, in which



Fig. 7.—A section through two corpora lutea, which was the only remaining ovarian tissue found in a rat that had a number of estrual cycles following double oöphorectomy.

both ovaries were left. In these three animals, the most regular cycles occurred to the date of death, thirteen months after operation.

It seems evident then from these experimental results that in animals in which the smallest amount of functioning ovarian tissue remained, the cycle showed the most irregularity, in some of them occurring entirely without rhythm.

The smallest bit of functioning tissue was obtained entirely by accident. On April 11, 1928, both ovaries were removed from several rats. Vaginal smears were taken daily after the operation as usual and on May 11, a positive smear was obtained from one of these rats. On

May 23, 24 and 26 and June 17, the smears were again positive. The animal was killed on July 2. There was in the region of the right ovary a small piece of tissue which appeared like tissue surrounding a ligature. In the region of the left ovary there was also a tiny bit of tissue; this had a yellowish cast and looked like ovarian tissue. Both these masses of tissue were saved and sectioned serially. The one from the right side revealed only fibrous tissue. The one from the left side showed two corpora lutea so close together that they appeared almost as one (fig. 7). This is the smallest bit of ovarian tissue which I have found would produce estrual periods.

#### CONCLUSIONS

It is concluded from this study that the ovaries of the rat can be severely traumatized without producing any effect on the estrual rhythm, that the amount of ovarian tissue can be considerably reduced and that the ovaries can be surrounded by adhesions so dense that the follicles apparently cannot rupture and expel their ova, without interfering with the estrual rhythm. But in cases in which the ovarian tissue is greatly reduced, irregularities of the estrual cycle occur, and if the amount of functioning tissue is reduced to a minimum, complete lack of rhythm is exhibited, consisting of short and prolonged periods of cornification with varying intervals between, strikingly similar to the complete irregularity of the menstrual cycle in women after operations on the ovaries. A study of the resulting ovarian pathologic changes after these operative procedures in the animal seemed to prove that one factor in the maintenance of normal estrual rhythm is certainly a sufficient amount of healthy ovarian tissue. It seems that estrum can occur without follicles being present in the remaining ovarian tissue, but in no instance did the cycle continue with neither follicles nor corpora lutea present. Brambell, Parkes and Fielding<sup>3</sup> have stated that the estrual cycle in mice is maintained with ovaries that do not contain follicles or corpora lutea, the ovaries having been treated with roentgen ray when the rats were 3 weeks old.

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3. Brambell, F. W. R.; Parkes, A. S., and Fielding, Una: Changes in the Ovary of the Mouse Following Exposure to X-Rays: I. Irradiation at Three Weeks Old, *Proc. Roy. Soc., London, ser. B.* **101**:29, 1927.

# SPONTANEOUS RUPTURE OF THE AORTA \*

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Spontaneous rupture of the aorta implies that partial or complete loss in the continuity of the vessel wall takes place without any evidence of extrinsic pathologic changes, trauma or formation of an aneurysm with secondary mural perforation.

The extrinsic causes of penetration of this large vessel are relatively frequent and such penetration must be differentiated from the true type. These include conditions producing erosion of the vessel wall from the external surface or surrounding structures; as tuberculous, inflammatory or malignant changes of the mediastinal or tracheobronchial lymph glands, carcinomatous or ulcerative lesions of the esophagus, destructive conditions of the vertebrae and malignant or inflammatory changes of the lungs.

Trauma in such form as to result in crushing of the thoracic cage occurs most frequently when the direction of the applied force is in the anteroposterior diameter of the chest. Numerous examples are recorded of large objects flying at a high velocity or a crushing between freight trains, etc., having resulted in tears of the large blood vessel. Jaffé and Sternberg<sup>1</sup> recorded the lesion as having occurred in six aviators who had fallen from high altitudes. The undue force exerted on the normal supporting structures of the aorta had resulted in tears in the artery in certain anatomic positions. The sites of predilection for the lesion will be discussed later.

In previous records of this lesion, the gross description of the vessel is usually given in sufficient detail to permit the conclusion that the vessel wall was not normal, but thorough microscopic descriptions are usually lacking. In two of the three cases to be reported, it is to be noted that the gross changes are not sufficient to explain the cause for the laceration, and that on histologic examination the alterations are considerably more marked than one is led to believe from macroscopic examination. Riley<sup>2</sup> reported a spontaneous rip of the thoracic aorta in a boy, aged 16, who had suddenly died while at work. The aorta was the site of a tear 1 cm. long, 2.5 cm. above the cusps on the left

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\* Submitted for publication, April 3, 1929.

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1. Jaffé, R. H., and Sternberg, H.: *Der Fliegertod: Ein Beitrag zur Frage der traumatischen Aortenrupturen*, Vrtljschr. f. gerichtl. Med. **58**:3, 1919.

2. Riley, De W. G.: *Spontaneous Rips of the Thoracic Aorta with Aneurysm*, Atlantic M. J. **27**:743, 1924.

lateral wall, which had ruptured into the pericardial sac; the latter contained about 100 cc. of blood. This was associated with a saccular aneurysm that was directed posteriorly. An anatomic diagnosis of status lymphaticus was made because the thymus weighed 60 Gm. and the mediastinal and abdominal lymph glands were hyperplastic. The other example noted by him was that of a 35 year old hunchback who fell down in a street-car and died in transit to the hospital. It was obtained that the spinal deformity had followed a fall in infancy, and that three months previously the patient had had lobar pneumonia. The autopsy revealed that the aorta was curved sharply to the right. On the convexity there was an aneurysm 4 by 1 cm., a slit 3.7 cm. long on the posterior wall, 1.8 cm. above the aortic ring, and an old slit, 2.5 cm. above the right extremity of the recent tear. In neither of these instances was a microscopic description recorded, but both vessels were undoubtedly the sites of considerable changes, as evidenced by the associated aneurysms in both and an old healed lesion in the latter. What influence the fall had on the hunchback with an already distorted aorta is a subject for theoretical discussion.

Usually the rupture takes place during moderate physical exertion, and is attributed to a concomitant elevation of the blood pressure. Paschkis<sup>3</sup> referred to a white man, 46 years of age, who collapsed while walking and died in four hours. The aorta,  $1\frac{1}{2}$  fingerbreadths above the valve, was ruptured longitudinally for a distance of 2.5 cm. The intima and media were penetrated but the adventitia was intact, and the latter was separated from the rest of the wall throughout the ascending and descending portions of the thoracic aorta. There was no perforation into the pericardial sac, but the latter contained a hemorrhagic fluid. Adjacent to the rupture there appeared to be a scar. He stated that microscopic examination of the wall revealed no changes and the Wassermann test of the blood was negative. Oppenheim<sup>4</sup> had a 53 year old patient with subacute glomerulonephritis, who died while on the toilet. Busse<sup>5</sup> reported an instance of death under the same circumstances. Bohnen<sup>6</sup> found a rupture 2 cm. above the aortic cusps and in the arch that occurred during severe labor pains. At the time, severe thoracic pain was complained of. The patient was 26 years of age. The autopsy demonstrated, in addition, fatty and calcific changes of the

3. Paschkis, K.: Ruptur der anscheinend normalen Aorta, *Med. Klin.* **21**: 1921, 1925.

4. Oppenheim, F.: Gibt es eine Spontanruptur der gesunden Aorta und wie kommt sie zustande? *München. med. Wchnschr.* **65**:1234, 1918.

5. Busse, O.: Ueber Zerreibungen und traumatische Aneurysmas der Aorta, *Virchows Arch. f. path. Anat.* **183**:440, 1906.

6. Bohnen, P.: Ueber einen Fall von Aortenruptur unter der Geburt und einen Fall von Septumdefekt, *Zentralbl. f. Gynäk.* **51**:2398, 1927.



basilar and carotid arteries and severe sclerosis of the ascending aorta. Bohnen here recorded that the elevation of the blood pressure at the height of labor pains may be from 60 to 100 mm. of mercury. The author cited four similar instances, and stated that rupture of the aorta had also occurred during eclamptic convulsions.

The condition can occur without physical exertion. Paschkis<sup>3</sup> quoted Süß in reference to a 48 year old patient whose aorta ruptured while he was lying in bed. The gross and the microscopic appearances of the vessel were regarded as normal.

The relation that trauma has to rupture of the aorta is of tremendous medicolegal importance; for if abnormal changes are present before the injury, the amount of the trauma necessary to produce the lesion can be very slight. In arriving at a judgment as to compensation, therefore, it is necessary that the condition of the artery, gross and microscopic, be taken into consideration. Gallagher<sup>7</sup> wrote on the occurrence of an aortic rupture in a 56 year old white man who was recovering from influenza and, in addition, had clinical evidence of aortitis with moderate dilatation of the heart and a blood pressure of 158 systolic and 106 diastolic. The aortic second sound was accentuated, and over the same area there was a loud systolic and diastolic murmur, and a systolic murmur over the mitral region. The patient died suddenly, and at the autopsy the aorta showed a ragged laceration just above the valves. The intima of the vessel was studded by numerous atheromatous plaques. The heart was surrounded by a layer of blood 2 cm. thick. Maitland<sup>8</sup> noted a tear 1 inch (2.5 cm.) long and  $\frac{1}{2}$  inch (1.27 cm.) distal to the site of the common carotid artery in a 49 year old man in whom the aortic second sound was not clear, and who developed evidences of cardiac decompensation following acute appendicitis complicated by deferentitis and funiculitis, and in whom later it was necessary to amputate the right leg because of gangrenous changes. His blood pressure was 160 systolic and 95 diastolic, and the Wassermann reaction of the blood was one plus. The significance of the infectious processes in the patients of Maitland and Gallagher cannot be stated.

Löffler<sup>9</sup> emphasized the underlying factor of nephritis. In both his patients, the aorta was not normal grossly and in the first patient hypertension was present with a reading as high as 224 systolic. In this patient there was a transverse laceration, 4 cm. long, in the ascending aorta, with a rip extending at right angles to it, which was 1 cm. long.

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7. Gallagher, E. T.: Rupture of the Aorta into the Pericardial Sac, U. S. Vet. Bur. M. Bull. **2**:972, 1926.

8. Maitland, C. D.: Spontaneous Rupture of the Aorta, Brit. M. J. **1**:79, 1925.

9. Löffler, W.: Ruptur der Aorta bei chronischer Nephritis, Cor.-Bl. f. schweiz. Aerzte. **48**:185, 1918.

The second patient, a man 43 years of age, had a systolic blood pressure varying from 160 to 180 and an enlarged heart. The aorta, 6 cm. below the ductus Botalli, was torn transversely for a distance of 8 mm. through the intima and media. It is to be noted in these two cases that undoubtedly other factors than nephritis must be taken in consideration.

Coarctation of the aorta with hypertension proximal to the occluded portion is a relatively frequent cause of spontaneous tearing of the aorta.

Nonsyphilitic ulcerations or focal inflammatory changes in any location in the aorta not infrequently occur, with destruction of all layers of the wall, and perforation takes place into the surrounding structures or extends between the layers of the aorta forming a dissecting aneurysm, which may even reenter the vessel at a different point.

That syphilitic mesa-ortitis sometimes is one of the underlying factors was observed by Uhles<sup>10</sup> in a woman 40 years of age, in whom cardiac decompensation was manifested over a period of years and eventually a left hemiplegia. On physical examination, the essential observations were an enlarged heart with a diastolic murmur over the aortic area, and a blood pressure of 248 systolic and 125 diastolic. Though her condition was improving under the administration of digitalis, she died suddenly while walking. The postmortem examination revealed 270 cc. of blood in the pericardial sac, and a left ventricle that was 20 mm. thick. The aorta was studded by numerous fatty and calcified plaques with an indented rupture 5 cm. long in the anterior wall, 1 cm. above the aortic cusps. This tear penetrated the media, but left the adventitia intact, except for a small opening that led into the pericardial sac. The microscopic diagnosis was syphilitic mesa-ortitis, slight sclerosis of the renal blood vessels and foci of encephalomalacia in the region of the central ganglions. Gsell<sup>11</sup> called attention to the frequent association of spontaneous rupture of the aorta with small areas of acute and recurring necrosis of the muscle fibers of the media. This necrosis may be syphilitic, but is observed also in cases in which syphilis can be excluded. For the latter instances, he assumed a nonsyphilitic infection or toxic injury of the aortic wall.

In the cases to be reported, it is to be noted that a combination of factors enters into the explanation of each of the spontaneous ruptures of the aorta.

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10. Uhles, B.: Ueber einen Fall von Aortenruptur mit Blutung in die Perikardhöhle, *Med. Klin.* **20**:49, 1924.

11. Gsell, D.: Necroses der Aortenwand als unabhängige Erkrankung und ihre Beziehung zur spontanen Ruptur der Aorta, *Virchows Arch. f. path. Anat.* **270**:1, 1928.

## REPORT OF CASES

CASE 1.—A colored man, 58 years of age, a laborer, entered the medical service of Dr. Harry Singer complaining of cough, swelling of the feet and shortness of breath over a period of four weeks. His past history revealed that he had been advised by a physician not to work because of some pathologic cardiac condition. He had had pneumonia twice, and at the age of 25 and again at the age of 30 he had had rheumatism. His wife had given birth to two children who were living and well, but she had had three miscarriages. In addition, the patient had had nocturia, being disturbed from three to four times a night for a period of several years. Physical examination revealed a poorly nourished colored man, orthopneic and coughing considerably. The temperature was 99.6 F., the pulse rate 104 and respiratory rate 26. The blood pressure was 198 systolic and 120 diastolic. The pupils did not react to light. In the right lower lobe, posteriorly, there were dry, coarse râles. The apex of the heart was located in the fifth intercostal space in the anterior axillary line, and the valvular sounds were rather rough, but no murmurs were present. The lower extremities were slightly edematous. The urine showed no abnormalities and the Wassermann reaction of the blood was negative. Roentgenologically, it was noted that the left ventricle was enlarged. The condition of the patient improved rather rapidly under the administration of digitalis and rest in bed. On the fourteenth day, he was able to be up and about, but at 10 p. m. he complained of considerable precordial pain, and became restless, noisy and short of breath. He died at 1:30 a. m.

Autopsy revealed a poorly nourished colored man. The abdomen was free from any changes, except that the lower margin of the liver was 1 fingerbreadth below the right costal margin and 3 fingerbreadths below the tip of the xyphoid process. In both pleural cavities there were fibrous bands attached to the mid-portion of the posterior aspect of the lungs extending to the parietal pleura, and the right side of the diaphragm was at the level of the fifth rib and the left side at the level of the sixth.

The heart, with the pericardial sac, and the aortic arch weighed 1,030 Gm. The pericardial sac was enormously distended; the left border was located in the midaxillary line, and the right, 3 cm. to the right of the right sternal border. The sac contained 300 cc. of a hemorrhagic fluid and a blood clot, from 2 to 3 cm. thick, which completely enveloped the heart. The heart was in a state of firm contracture, and on the epicardium was an irregular, round, white area, 2 cm. in diameter, on the anterior aspect of the left ventricle, 3 cm. below the base. The myocardium was firm and a light reddish brown. The diameter of the left ventricle was 10.5 cm. Considerable flattening of the trabeculae near the apex and thickening of the endocardium over the left side of the interventricular septum were present. Several dark red patches were seen in the subendocardium of the anterior wall of the left auricle, the largest measuring 1 cm. in diameter. Similar smaller patches were present in the wall of the right auricle just above the attachment of the middle cusp of the tricuspid valve.

The aorta above the valves measured 82 mm., and there were numerous slightly elevated, irregular, light yellow plaques above the aortic cusps. Three centimeters above the valve was a transverse rupture of the aortic wall, which involved the entire circumference of the vessel. The edges of the tear were smooth, and near the left end of this defect was another tear 3 cm. long, extending in the longitudinal axis of the ascending aorta. This formed a triangular flaplike structure, the tip of which extended upward to within 1 cm. of the innominate artery. The portion of the aorta distal to the laceration was retracted upward for a distance of 2 cm.; thus the wall of the vessel, in this portion, consisted of

adventitia only, which was lined on the inside by blood clot and small, grayish-white tags. In the direction of the valve, the adventitia was completely separated from the other parts of the aorta, and the space between the aorta and the pulmonary artery was filled by dark red blood clots. These surrounded an opening in the adventitia which had a diameter of 20 mm. and led into the pericardial sac. The edges of the opening were indented, and the defect itself was crossed by a fibrous strand. The peripheral part of the ruptured aorta was practically closed by the separated intima, which was pushed as a duplicate fold into the lumen. The

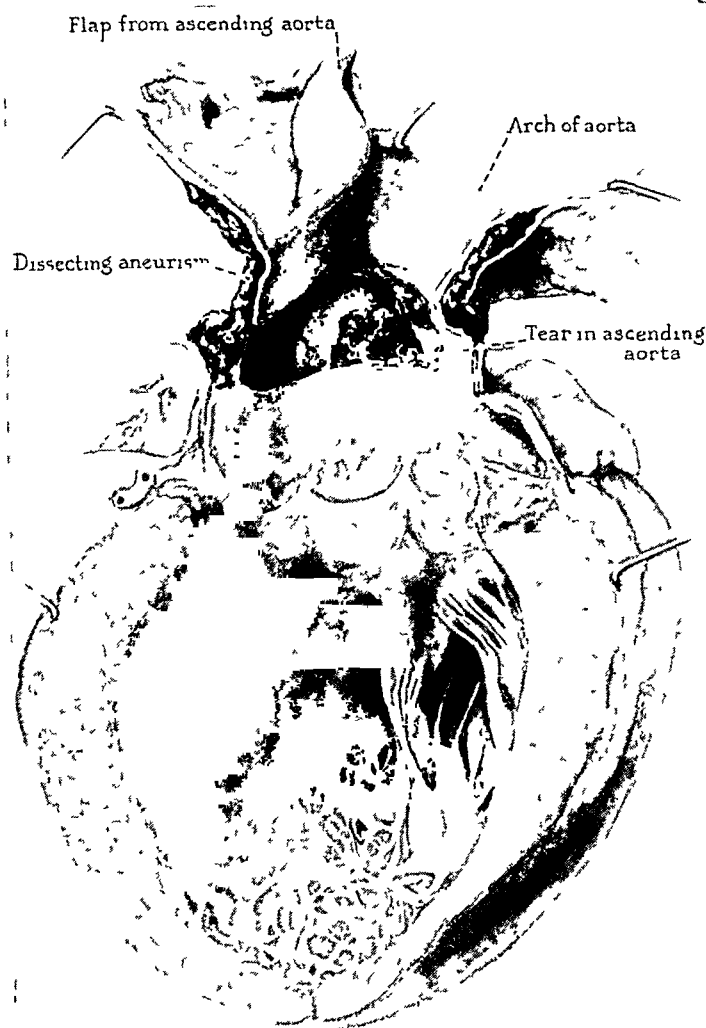


Fig. 1.—A spontaneous tear of the aorta, 3 cm. above the aortic cusps, with only slight atheromatous changes in the supra-ventricular region.

descending aorta was wide, with a circumference of 60 mm. at the diaphragm and of 42 mm. at its bifurcation. The intima was studded by numerous irregular, linear depressions, which were most abundant near the arch, where there was a moderate number of flat, yellow plaques, which also extended through the aorta and into the larger blood vessels. The descending thoracic portion was the only region in which there was a moderate amount of wrinkling and puckering of the intima.

The liver weighed 1,520 Gm. The surface was reddish brown, and the surfaces made by cutting showed distinct markings and were wet with blood. The gallbladder contained three stones shaped like mulberries, and ranging in diameter up to 8 mm.

The spleen weighed 99 Gm. The surface was wrinkled, and there was an increase in the fibrous elements throughout the substance.

The lungs were crepitant throughout. They were devoid of any changes.

The kidneys together weighed 230 Gm. Their external surfaces were reddish brown and slightly granular, and there were several cortical cysts varying from 2 to 5 mm. in diameter.

*Microscopic Examination.*—Several sections taken from the edges of the tear in the aorta revealed numerous capillaries extending from the adventitia into the media, which were surrounded by accumulations of lymphocytes and plasma cells. In the media were, also, numerous areas of calcification, and in the intima deposits of lipid material. Other sections taken from the arch were free from changes.

Sections removed from the left ventricle of the heart showed numerous accumulations of myocytes in nodular arrangement (Aschoff bodies) about the medium-size arteries.

The medium-size arteries of the kidneys, and especially the smaller ones, were considerably sclerosed, resulting in narrowing of their lumen, and there were foci of atrophy and compensatory hypertrophy.

*Comment.*—The patient presented clinical evidence of cardiac decompensation following an infection of the upper respiratory tract, associated with enlargement of the heart and hypertension secondary to sclerosis of the medium-sized and smaller arteries. His response to the administration of digitalis and to rest was rapid, permitting him to be up and about. Then he suddenly suffered the rupture of the ascending aorta, with perforation into the pericardial sac. The factors predisposing to the lesion were: the disease process in the aorta, the hypertension with marked hypertrophy of the left ventricle, the renewed physical exertion and possibly the administration of digitalis. The gross appearance of the ascending aorta lent the impression that the vessel was the site of atheromatous changes only, but the microscopic examination revealed the presence of syphilis, which was more or less confined to the site of the rupture. This emphasized the importance of examining various regions of the vessel and particularly that near and including the defective portions. However, the possibility of rheumatic aortitis cannot be excluded in view of the work of Pappenheimer and von Glahn,<sup>12</sup> who demonstrated lesions in the aorta associated with acute and chronic rheumatic myocarditis. In these sections of the vessel, the syphilitic changes may have obscured the microscopic pathologic changes. Associated with these changes of syphilitic and possibly rheumatic origin was the presence of considerable amounts of lipoids in the intima with small areas of calcium deposits. These inflammatory and degenerative changes undoubtedly markedly altered the functional capacity of the muscular and elastic tissues of the involved regions and as a result the dilatability of this portion of the aorta was markedly diminished. The added load of a compensating heart, together with the increased muscular power of the left ventricle as the result of treatment with digitalis, and the physical effort of being up and about were sufficient to rupture the already damaged elastic and muscular fibers.

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12. Pappenheimer, A. M., and von Glahn, W. G.: Lesions of the Aorta with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Fever, *J. M. Research* **44**:489, 1923-1924.

CASE 2.—This patient entered the Grant Hospital on the service of Dr. J. E. Siebel on Oct. 5, 1928. She was an Italian woman, married, 41 years of age, who on the day of admission, while eating lunch, complained of severe precordial pain, became short of breath, fainted and was immediately sent to the hospital. Anuria was present for the first twenty-four hours, and she was semicomatose at times during the first day. Her previous history revealed that she had had severe headaches for a few weeks past. However, there had been no previous dyspnea or precordial pain. Her blood pressure on the day following admission was 178 systolic and 134 diastolic. The temperature varied from 98 to 101 F., the pulse rate fluctuated from 82 to 120 during the four days before her death, and the respiratory rate increased from 22 to 36. Roentgen examination of the chest showed marked enlargement of the cardiac area.

The autopsy, for a report of which I am indebted to Dr. S. Brown, revealed an obese, pale white woman, weighing about 190 pounds (86.2 Kg.), with a thick and short neck. In the abdominal cavity there was about 500 cc. of clear, straw-colored fluid and in each pleural cavity 1,000 cc. of a similar fluid. About the apex of the right lung and the base of the left were numerous fibrous adhesions. The pericardial sac was filled with blood and was firmly adherent to the left lung through fibrous adhesions. There were a few scars in the pleura of the lungs. In the right pulmonary apex and in the middle of the left base was a subpleural nodule, 1 cm. in diameter, which was partially calcified and filled by yellowish-white material. The remainder of the lungs was dry.

The heart, with the attached pericardium, and 8 inches (20.32 cm.) of the aorta, weighed 685 Gm. The aorta, externally, appeared dilated, and on being opened revealed a transverse slit in the intima and media, two fingerbreadths above the aortic ring and involved all except 1 cm. of the circumference of the aorta. Extending to the left and posteriorly and opening into this slit was a sac the size of an egg, the wall of which was thin and lined by firm, deep red blood clots. In one of the thinnest places of the wall was an opening of pinhead size leading into the pericardial sac. The entire outpouching was within the pericardial sac. The lining of the aorta, above and below the rupture, was smooth except for a few small fatty plaques. On the inferior convex surface of the transverse aorta were two fatty plaques, each 1.5 cm. in diameter. The coronary orifices and the vessels were patent. Numerous punctiform hemorrhages were present in the subepicardial tissues. The myocardium of the left ventricle averaged 20 mm. in thickness and was pale brown, and the papillary muscles were thickened.

The liver weighed 1,745 Gm. and was soft. The surface made by cutting had distinct acinar markings and was pale brown and mottled yellowish white. The gallbladder contained thick, golden-yellow bile.

The spleen weighed 231 Gm. The capsule was wrinkled and the pulp dark red.

The right kidney weighed 231 Gm., and the left 302 Gm. The capsules stripped easily, leaving a pale, slightly granular surface. The parenchyma was pale and the markings were indistinct.

The suprarenal glands were large and the cortex and medulla were moderately increased.

*Microscopic Examination.*—In the outer third of the media of the aorta (above the rupture) there were single dilated capillary blood vessels surrounded by small groups of lymphocytes, swollen histiocytes and a few plasma cells. The intima was thickened by large deposits of cholesterol esters and fatty-acid needles located near the media; the fatty changes extended into the media, and there were numerous lipoid granules about the elastic fibers of the media. The adventitia was

thickened and slightly sclerosed, and there were loose accumulations of lymphocytes and plasma cells. The blood had broken into the media, separating the outer from the middle third. Recent hemorrhages were found in the adventitia. Where the capillaries invaded the media, the elastic fibers were spread apart, and in places the continuity was interrupted.

The large plaque near the ductus botalli was composed of hyaline connective tissue with large deposits of lipoids in the deeper parts of the media, which also contained capillaries surrounded by lymphocytes.

In the aorta (below the rupture), the intima and the internal two thirds of the media were separated from the rest of the wall by a large recent hemorrhage, composed of fibrin, platelets, erythrocytes and numerous leukocytes.



Fig. 2.—An incomplete transverse tear,  $1\frac{1}{2}$  fingerbreadths above the aortic cusps, with marked hypertrophy of the myocardium of the left ventricle.

The kidneys showed distinct thickening of the walls of the arterioles and small subcapsular scars in the cortex. Bowman's spaces of the glomeruli were dilated and filled with palely stained and finely granular material. Bowman's capsules were thickened. The muscle fibers of the myocardium were distinctly thicker than normal, and their nuclei had irregular shapes and contained much chromatin. The cross-striations were obscured.

*Comment.*—In this instance, the lesion occurred, although there evidently were no symptoms referable to any pathologic cardiac or vascular changes and the precordial pain was not so severe as in the first patient and the course following the rupture was more prolonged, owing to the fact that the opening from the aorta into the pericardial sac was considerably smaller, thus causing a more gradual compression of the heart. The pathologic changes in this case are of marked importance in that the gross appearance did not suggest the possibility

of syphilitic changes, but the microscopic alterations were relatively marked, particularly in the region of the rupture. The factor of hypertension again played an important rôle in causing local destruction in the already damaged vessel wall. In addition to the syphilitic process, considerable lipoid degeneration had to be taken into consideration.

CASE 3.—A colored man, 56 years of age, entered the medical service of Dr. Sidney Portis, in the Cook County Hospital, on Feb. 7, 1929. The patient said that he had been in good health until the year 1926; then he had become short of breath; this complaint had increased in severity, so that in December, 1928, he was unable to sleep when flat on his back, and his ankles had become edematous. In the three years before his entrance, he had lost 25 pounds (11.3 Kg.) in weight. Thirty years previously he had had a chancre, for which he had not received any antisymphilitic treatment.

Physically, he was well developed and well nourished but was very short of breath. His temperature was 98 F., his pulse rate 102 and his respiratory rate 26 per minute. The blood pressure was 180 systolic and 120 diastolic. The aortic dulness was markedly increased toward the left. The cardiac apex was in the eighth intercostal space in the midaxillary line, and the right border of the heart was 1 inch (2.5 cm.) to the right of the right sternal border. There was a systolic and diastolic murmur over the mitral area. The edge of the liver was palpated 5 fingerbreadths below the right costal margin. Marked edema of the lower extremities was present. The Wassermann test of the blood was negative. The content of urea nitrogen in the blood and the urine was free from any significant changes. During the five days that he was in the hospital before his death, he received 20 drops of tincture of digitalis three times a day and was kept at absolute rest. His pulse, however, became irregular. He was restless and gradually passed into a comatose state and died without any complaint of precordial distress.

The essential observations at autopsy revealed a well developed and well nourished colored man with purplish discoloration of the skin of the head, neck and finger-tips. The veins of the upper thoracic and cervical regions were markedly distended by blood. The lower extremities were edematous. About the right upper and the left lower pulmonary lobes were fibrous adhesions, and in the right pleural cavity was 400 cc. of clear, straw-colored fluid. The pericardial sac extended from the right costochondral junction to the left anterior axillary line.

The heart weighed 600 Gm. Both ventricles were dilated, the left ventricle measuring 10 cm. transversely and 12 cm. longitudinally. The myocardium of the left ventricle was 22 mm. thick and that of the right 6 mm. thick. The heart muscle was rather friable and pale brown-gray. The trabeculae in the left ventricle were markedly flattened. In the coronary arteries were a few slightly elevated, yellowish-white plaques.

The aorta was markedly dilated, having a circumference of 95 mm. in the supravalvular region, 60 mm. at the level of the diaphragm, and 46 mm. at its bifurcation. The intima of the ascending portion was smooth except for a few flat, light yellow plaques, which varied from 3 to 7 mm. in diameter. On its anterior aspect, 20 mm. above the right aortic cusp, was a flat circular depression 5.5 cm. in diameter. At the upper edge of this depression, just below the innominate artery, was a roughly triangular defect in the wall with its apex directed downward, having a base 5 cm. across and a vertical measurement of 4 cm. This defect was surrounded by a smooth and partially undermined edge and its floor was composed of firm, whitish tissue, which gradually merged with the surrounding aortic wall. At the lower angle of this triangular area was an oval opening,



2.5 by 1.5 cm., which led into a semicircular sac having a diameter of 6 cm. and a depth of 3 cm. This sac was located within the pericardial sac and was adherent to the anterior and right lateral wall of the ascending aorta. This cavity was filled by soft, dark red blood clots and its outer surface was gray-brown and covered by thin fibrous tags.

In the arch of the aorta, in the region of the left subclavian and carotid arteries, there was a transverse ring of light yellow plaques, which was from 5 to 7 mm. wide. Between the plaques were fine, irregular, linear depressions.

In the descending aorta, 5 cm. below the opening of the left subclavian artery, there was a circular opening, 5 cm. in diameter, located in the left latero-anterior portion of the wall. This opening led into a large cavity that bulged into the left upper pulmonary lobe. The cavity was 7 cm. deep and 9 cm. longitudinally by 8.5 cm. transversely; it was filled by dark-red blood clots and compressed the left main bronchus, which was filled by thick mucopurulent material. The upper portion of the left upper lobe was airless, but the remaining lung substance was subcrepitant. The lining of the descending aorta was smooth, except for a few small, yellow plaques and linear depressions. There was another irregular opening, near the celiac artery, located on the anterior aspect of the aorta, which was of triangular shape, having a base 20 mm. in width and measuring 30 mm. longitudinally. This opening extended upward for a distance of 1 cm. beyond the junction of the thoracic and abdominal portions. This defect contained soft, deep red-gray blood clots, which separated the intima and the media from the adventitia. Two centimeters below this opening was a longitudinal slit 30 mm. long, located 10 mm. to the left of the superior mesenteric artery and extending downward to the region of the renal arteries. Near these tears were numerous flat, yellow-white plaques from 3 to 5 mm. in diameter.

The kidneys together weighed 300 Gm., and contained numerous cysts from 5 to 15 mm. in diameter that replaced much of the renal parenchyma. The capsules were slightly adherent to a dark purplish-gray surface that was studded by pink-gray and gray-white nodular elevations from 1 to 3 mm. in diameter. The cortex was 5 mm. wide and gray-brown, and the markings were obscure. Microscopically, there were marked hyalinization and lipoid infiltrations of the arteriolar walls. The majority of the glomeruli were well preserved, but a few were obliterated by hyaline material.

*Microscopic Examination.*—The flat, circular, depressed area in the ascending portion of the aorta revealed typical syphilitic changes and, in addition, the adventitia was irregularly separated from the media. The latter was markedly altered in that the normal stratification of the muscle fibers was lacking, and had been partially replaced by irregular round areas of myxomatous-like tissue. The nuclei in these portions assumed a whorl-like arrangement in the peripheral zones, whereas in the central areas their arrangement was irregular and they varied in size and shape in that they were elongated, round, triangular or stellate in outline. This type of tissue extended toward and formed the inner wall of this portion of the ascending aorta and there was no intimal lining present in this area.

*Comment.*—In this patient, the clinical manifestations of gradual cardiac decompensation extended over a period of about three years. There was a history of primary syphilitic infection thirty years previously and, in addition, marked hypertension with cardiac hypertrophy most likely secondary to the arteriosclerosis of the kidneys. In spite of the fact that there were a healed lesion and two recent ruptures in the aorta, the patient presented no clinical indications of these pathologic conditions.

## SUMMARY

In these three instances of spontaneous rupture of the aorta, it is to be noted that although the vessel may be free from extensive gross inflammatory or degenerative changes, nevertheless, as microscopic examination demonstrates, considerable destruction of the vessel wall may have occurred in places, and it is at these points that the vascular wall has a tendency to tear. However, other conditions must also be taken into consideration in that frequently the aorta is the site of extensive degenerative and inflammatory changes. Nevertheless, spontaneous rips do not occur frequently. Sudden increase in the blood pressure as the result of renewed physical exertion, excessive exertion and possibly the administration of digitalis play important rôles in the causation of tears in diseased aortas.

From the foregoing correlation of gross and microscopic alterations in the aortic wall, it is obvious that careful microscopic examination is necessary in all instances, especially, of the edge of the rupture. Legally, the latter observation should be taken into consideration when the lesions occur following various amounts of trauma.

As is so frequently the occurrence in syphilitic aortitis, the Wassermann reaction of the blood was negative in two of the three instances reported, and in the third there was no examination of the blood by either the Kahn or the Wassermann method.

Most frequently, the rupture of the aorta occurs either  $1\frac{1}{2}$  finger-breadths above the aortic cusps or in the region of the ductus botalli, whether the condition has occurred spontaneously or following trauma. Various reasons for this choice of site have been tendered, but that of Rindfleisch<sup>13</sup> is most generally accepted, namely: first, there is a fibrous union between the ascending aorta and the pulmonary artery which serves as a fixed point, and second, there is an obliteration of the ductus arteriosus with fixation of the aortic arch. The portions of the aorta surrounding these regions are relatively movable and therefore the vessel tears at the two points of fixation.

That healing can occur following a spontaneous rip of the aorta is exemplified in the last reported instance, which microscopically shows a healing process characteristic of a wounded or lacerated vessel wall.

Although this lesion occurs most frequently at the points of fixation of the thoracic aorta, the last case presented two tears below the diaphragm. However, the local destruction in these areas was marked and the blood pressure was high.

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13. Rindfleisch, E.: Zur Entstehung und Heilung des Aneurysma Dissecans Aortae, Virchows Arch. f. path. Anat. **131**:174, 1893.

## CONCLUSIONS

1. Spontaneous rupture of the aorta occurred in three instances  $1\frac{1}{2}$  fingerbreadths above the aortic cusps, and in one of these there were two tears of the vessel below the level of the diaphragm.

2. The gross changes at the site of such a rupture are frequently inadequate to explain the tears, but localized microscopic alterations of a syphilitic and degenerative nature are marked.

3. Medicolegally, microscopic examination at the site of the rupture is important.

4. A combination of contributing factors must be taken into consideration, which include the local destructive process and the conditions that increase the blood pressure. The latter may be on an arteriosclerotic, nephritic, functional or therapeutic basis.

# THE STRUCTURAL CHANGES OF THE LIVER IN PERNICIOUS ANEMIA

A CONTRAST BETWEEN RELAPSE AND REMISSION\*

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Medical science has taken a great stride with the contribution in 1926 by Minot and Murphy on the treatment for pernicious anemia with the ingestion of large amounts of liver or kidney. This treatment promptly, rapidly and with regularity benefits strikingly the health of most patients with this disease. The number of red blood cells returns to normal and is maintained at that level if proper amounts of liver or a potent substitute are taken. Cohn, with Minot and Murphy and their associates,<sup>1</sup> showed that an extract of liver produces the same results, and that the active principle is probably a nitrogenous base which acts to promote the growth of the primitive cells which crowd the bone-marrow in relapse. Consequently, a method to relieve the patient with pernicious anemia is now known, and something has been learned of the nature of the substance essential for recovery. A further advance has been made by Castle,<sup>2</sup> who demonstrated that whereas the ingestion of 200 Gm. of beefsteak has no effect on pernicious anemia, the anemia may be promptly alleviated by the daily feeding of 200 Gm. of beefsteak predigested in a normal stomach. This indicates that normal gastric juice, although by itself incapable of such action, is essential for the elaboration of this curative substance from meat, and suggests that the achylia gastrica which is always present in this disease may be an etiologic factor. The primary etiology of pernicious anemia, however, remains obscure, and investigators are still in the dark with regard to the forces which bring about the various pathologic alterations in the body.

One may speculate on the probable substance or substances essential for the maintenance of the normal composition of the blood. Whether the changes occurring in pernicious anemia are due to a failure of the elaboration of a hypothetic substance or substances, or whether the anemia and other bodily changes are due primarily to constitutional or

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\* Submitted for publication, April 24, 1929.

\* From the Thorndike Memorial Laboratory of the Boston City Hospital.

1. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: *Treatment of Pernicious Anemia with Liver Extract*, Am. J. M. Sc. **175**:599, 1928.

2. Castle, W. B.: *Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia*, J. Clin. Investigation **6**:2, 1928.

acquired factors, remains to be established. The various links in the chain necessary for a complete understanding of the nature of pernicious anemia will be obtained only by careful study of the disease from its inception through the various stages of relapse, remission and return to an apparently normal condition. Among the factors that some investigators have thought important in the etiology of the disease is the state of the liver; thus, a review of this topic seemed desirable. The pathologic histology of the liver in twenty patients not treated with liver, and in five treated with liver, who died from intercurrent disease while in partial or complete remission, is the subject of this paper.

It is conceded usually that Combe<sup>3</sup> in 1822 recorded the first case that was presumably one of pernicious anemia. His record of the liver is that it was light brown. Addison,<sup>4</sup> neither in his original article (1849) nor in his monograph in 1855,<sup>5</sup> made any statement as to the pathologic changes of the liver. In 1857, Samuel Wilkes<sup>6</sup> reviewed the postmortem observations of a group of cases and was impressed by the presence of an increased amount of fat in some, but not in all, of the livers.

The first important contribution to the pathologic condition of the liver in pernicious anemia was made in 1877 by Quincke,<sup>7</sup> who noted that there was an increased iron content in this organ, to which condition he gave the name siderosis. The significance of this, however, was masked in his mind by the knowledge that the patient had been treated with iron, and he thought that the ingested iron was the cause of the siderosis. William Hunter,<sup>8</sup> in 1889, was the first to stress the importance of the iron-containing pigment in the liver and other tissues. He accumulated data to show that there was a considerable increase in the iron content of the liver in pernicious anemia over that normally present and an amount in excess of that occurring in most other anemias.

Textbooks on general pathology state little about the liver in pernicious anemia. They usually record that fatty degeneration may be found in some cases, but that siderosis of the liver is a characteristic

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3. Combe, J. S.: History of a Case of Anemia, Tr. Med.-Chir. Soc. Edinburgh, May, 1822.

4. Addison, T.: Anemia: Diseases of the Suprarenal Capsules, London M. Gaz. **43**:517 (March) 1849.

5. Addison, T.: Idiopathic Anemia: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules, London, S. Highley, 1855.

6. Wilkes, Samuel: Cases of Idiopathic Fatty Degeneration, Guy's Hosp. Rep. **3**:203, 1857.

7. Quincke, I.: Weitere Beobachtungen über pernicioser Anämie, Deutsches Arch. f. klin. Med. **20**:1, 1877.

8. Hunter, William: On the Pathology of Blood Destruction within the Liver, Tr. Med.-Chir. Soc. Edinburgh, April 1887; Pernicious Anemia, London, Charles Griffin & Company, 1901.

feature and that foci of focal necrosis may occur. In addition to this, one often finds quoted the observation of Meyer and Heineke,<sup>9</sup> in 1907, that accumulations of myelocytes and erythroblastic cells may be found in the liver. Other authorities, except Piney, added nothing further in regard to blood formation in the liver in pernicious anemia. In 1925, Piney<sup>10</sup> wrote that "in all cases of pernicious anemia it is possible to find intravascular islets of pure megaloblastic tissue in the hepatic capillaries, and their arrangement is identical with that seen in the embryo." There is but little reference in the literature to the morphology of the Kupffer cells in pernicious anemia. Moffitt<sup>11</sup> stated that hypertrophy of these cells occurs.

#### THE LIVER OF PATIENTS DYING IN SEVERE RELAPSE FROM PERNICIOUS ANEMIA

The observations here recorded were made on twenty patients with pernicious anemia who were not given liver therapy and who died with profound anemia.<sup>12</sup> The material studied consisted of sections of liver from each patient, cut from paraffin blocks and stained with eosin and methylene blue (methylthionine chloride, U. S. P.). A general survey of the tissue was made with the low power microscope, while the finer details were studied with the oil immersion lens. The entire field of the tissue was covered during the examination. The examination was conducted with the following subjects particularly in mind: the size of the Kupffer cells and whether they contained pigment and phagocytosed red blood cells; the amount of siderosis of the liver cells; the presence of erythropoiesis; the occurrence of megaloblasts in the sinusoids and the amount of fatty degeneration, focal necrosis and periportal infiltration.

At the time of death the red blood cells in all except two cases numbered less than 1,000,000 per cubic millimeter; in two cases the count was about 1,500,000 per cubic millimeter.

Marked enlargement of the Kupffer cells was found in each of the twenty cases. The increase in size was due both to an abundance of cytoplasm and particularly to a swelling of the nucleus, so that the cells bulged well out into the lumen of the capillaries. This enlargement was not limited to scattered cells or groups of cells, but was found to be characteristic of all the Kupffer cells and was most apparent in those

9. Meyer, E., and Heineke, A.: Ueber Blutbildung bei schweren Anaemien und Leukaemien, *Deutsches Arch. f. klin. Med.* **88**:435, 1907.

10. Piney, A.: Some Morphological Factors Governing the Incidence of Pernicious Anemia, *Proc. Roy. Soc. Med.* **18**:5, 1925.

11. Moffitt, H. C.: Studies in Pernicious Anemia, *Am. J. M. Sc.* **148**:817, 1914.

12. These cases appear in the hospital record prior to 1926, and, therefore, before the introduction of liver therapy.

cells which had been cut through the central longitudinal plane rather than the periphery. Phagocytosis of red blood cells was present to a moderate degree and was recognized by the presence of whole or disintegrating cells within the protoplasm. The majority of the cells, and principally those at the outer two thirds of the lobule, contained a yellowish-brown pigment.

Not infrequently one end of a Kupffer cell was seen to lie free in a sinusoid while the other end appeared still to be attached to the reticu-

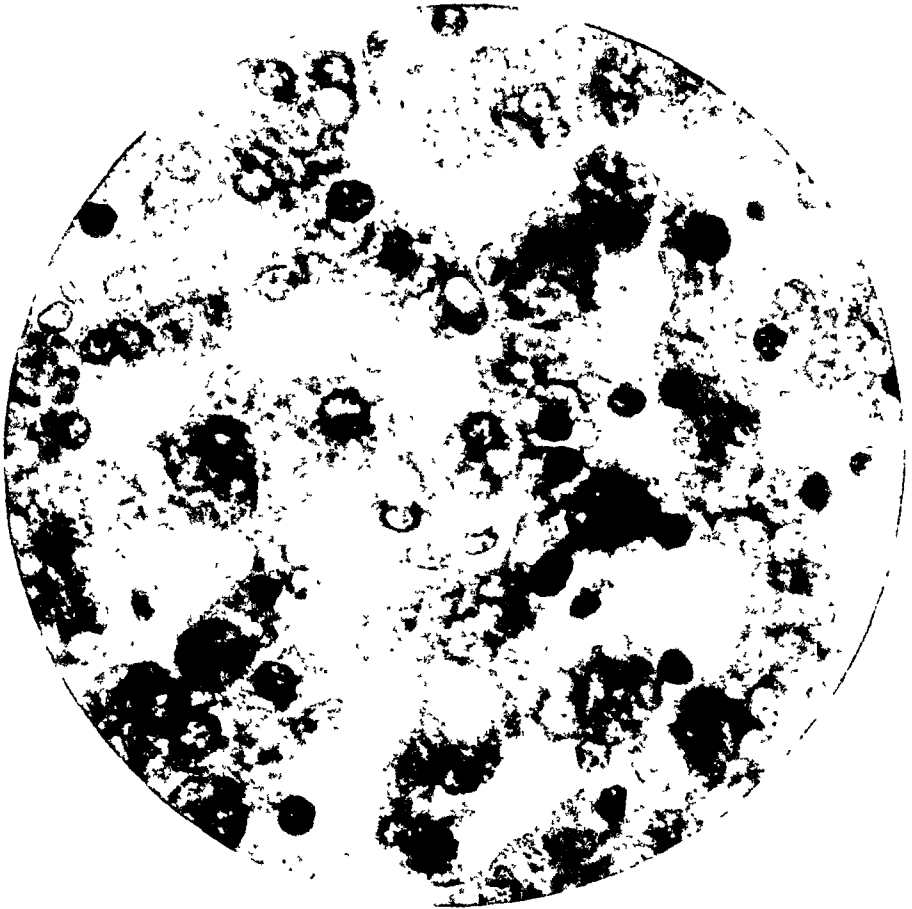


Fig. 1.—The liver in pernicious anemia during a severe relapse;  $\times 750$ . The pronounced hypertrophy of the Kupffer cells should be noted. Slight fatty degeneration of the liver cells is present.

lum. Such cells apparently were in the process of desquamation. This was made all the more apparent by a study of the cells in the sinusoids, in which there were large numbers of phagocytes. Here they appeared as a single nucleated, round or oval mass of pink-staining protoplasm. There extended from some of the phagocytes a finger-like pseudopod, while others were stretched out as a long slender mass within the capillary. Cells of this sort were all laden with yellow-brown granules of hemosiderin, and with whole and disintegrating red blood cells.

A yellowish or yellowish-brown pigment, evidently hemosiderin, was also found distributed about the periphery of the lobules of the liver and principally in the parenchymatous cells. It was most densely concentrated on the side of the cell adjacent to the bile canaliculi.

In order especially to compare the state of the Kupffer cells in other conditions with those in pernicious anemia, sections of liver were studied from subjects who died from various infectious processes. These were selected in no way and represented routine autopsy material. Included were miliary tuberculosis, chronic bronchitis, tonsillitis, acute peritonitis and subacute endocarditis. In addition, sections of liver from a case of aplastic anemia and from two cases of myelophthisic anemia were studied. In all these cases, the patients had died of a terminal pneumonia. In these livers an occasional hypertrophied Kupffer cell was seen, but for the most part the cells were small and slender. A varying number of desquamated and phagocytic cells in the sinusoids and slight phagocytosis of red blood cells were noted. This reaction, however, was a response of the "reticulo-endothelial system" to infection, and the hypertrophy of the Kupffer cells was certainly slight in comparison to the marked general hypertrophy which occurs in pernicious anemia, although the desquamation of the Kupffer cells and phagocytosis was about equivalent.

In spite of critical examination of the centrally and peripherally placed sinusoids, the space between the parenchyma of the liver and the reticulum of the sinusoids, and the periportal connective tissue, no signs of erythropoiesis were observed in any of the sections from the twenty cases.

It must be borne in mind that in fixed tissues stained with eosin and methylene blue, it is difficult to differentiate the various mononuclear cells. In seventeen of the twenty cases, a comparatively large cell was present in the sinusoids with a moderate amount of blue-staining protoplasm that contained a large round nucleus. The latter was surrounded by a definite basophilic membrane which enclosed a moderate amount of chromatin with a "spoke-wheel" type of arrangement, giving it a reticular appearance; this differentiated it from the monocyte and its larger size from the plasma cell. Such cells seemed to be megaloblasts and did not occur in clumps but only appeared free in the sinusoids. No islets of erythroblastic cells were found such as occur in the liver with extramedullary blood formation.

Fatty degeneration of varying degrees was seen in seven of the cases studied, but the process was never extensive. In seven cases, foci of necrosis were observed, while four showed a slight degree of chronic passive congestion. Fatty degeneration and focal necrosis, however, are not specific features of pernicious anemia as similar changes occur in many other conditions.



Periportal infiltration of lymphocytes and plasma cells with an occasional polymorphonuclear eosinophil were found in seven cases. This condition probably is not of any great significance, but should not be confused with myeloid metaplasia.

THE LIVER OF PATIENTS TREATED WITH LIVER WHO DIED FROM  
INTERCURRENT DISEASE DURING REMISSION

Several sections of liver were studied from each of five patients who died while in a stage of remission of pernicious anemia produced by liver therapy. The sections were prepared and inspected in the same manner as those from the former group. The salient facts pertinent to the state of the liver regarding these five cases of typical pernicious anemia are recorded below.

CASE 1.—A white man, aged 57, had a red blood count of 655,000 per cubic millimeter and bronchopneumonia at the time of entry to the hospital. Raw liver pulp derived from 250 Gm. of liver was given that day. On the subsequent days until death the patient was fed liver pulp from about 550 Gm. of liver. On the sixth day, the reticulocytes had risen from 0.4 to 18 per cent. Despite a transfusion of blood and symptomatic therapy the pneumonia became more extensive, and on the eighth day, at which time the reticulocytes amounted to 23 per cent, the patient died.

CASE 2.—A white woman, aged 60, first entered the hospital three years before death, with typical pernicious anemia. She was put on an adequate liver diet, and in due time her blood returned to essentially normal. A year before death she decided to reduce her weekly ration of liver to an amount derived from three quarters of a pound. A month before death severe diarrhea developed, and at this time she stopped taking liver. Acute bronchitis and acute cystitis were present when she entered the hospital for the last time. The hemoglobin content was 26 per cent, and the red blood cells numbered 992,000 per cubic millimeter. The reticulocytes numbered 0.8 per cent. She was given daily doses of liver extract no. 343 derived from 400 Gm. of liver. On the ninth day, the reticulocytes had risen to 17 per cent. Pneumonia developed, and the patient died on the eleventh day after the doses of liver extract were commenced.

CASE 3.—A white woman, aged 58, entered the hospital with profound anemia. She was put on a liver diet, and the blood showed prompt improvement. Five months later she was brought back to the hospital in a dying condition, suffering from lobar pneumonia of which she died two days later. The day before death the red blood cells numbered 3,700,000 per cubic millimeter and the hemoglobin content was 70 per cent.

CASE 4.—A white man, aged 57, entered the hospital with a red blood cell count of 1,600,000 per cubic millimeter; the hemoglobin content was 35 per cent. The daily administration of the pulp from 300 Gm. of raw liver was followed by a reticulocyte response of 19 per cent on the seventh day and a rapid rise in the concentration of the red blood corpuscles. He maintained an adequate liver diet at home with evidence that the number of red blood cells became normal. Thirteen months later, he was brought to the hospital in a dying condition, at which time the blood appeared normal; he died the following day from a widespread phlebitis involving the iliac veins, vena cavae and mesenteric veins.

CASE 5.—A man, aged 65, had had a partial prostatectomy eight years before the present entry. One and a half years before death, it was necessary to remove more of the prostate because of progressive obstruction, and he was found to have some urinary infection. Evidence of malignancy was not obtained from the examination of the tissue. It was learned at this time that for the past six months he had some numbness of the hands, and he said that he had "much dyspepsia" all his life. Studies revealed that he had symptoms and signs typical of pernicious anemia. The red blood cells numbered 2,400,000 per cubic millimeter, and the hemoglobin content was 60 per cent. He was put on a diet of liver extract no. 343, and



Fig. 2.—The liver in pernicious anemia during a remission. The Kupffer cells appear normal and are short and slender.

within two months the red blood cells amounted to 5,500,000 per cubic millimeter, and the hemoglobin content was 95 per cent. The red blood cells remained at a normal level until two months before death when they numbered 4,000,000 per cubic millimeter. Three weeks before his death from lobar pneumonia, the red blood cells numbered 4,500,000 per cubic millimeter. At autopsy, a carcinoma of the prostate with invasion of local tissues was found.

These cases, therefore, represent different stages and degrees of remission of pernicious anemia at the time of death. In two cases the remission had just commenced. In one patient, who was treated five

months, either the red blood cells had fallen rapidly before death owing to infection, or the patient had taken insufficient liver and had thus not had a complete remission. She was, however, in a state of at least moderate remission. The two other patients died when their blood was essentially normal.

#### COMMENT

The most striking distinction between the livers of the patients treated with liver and those not so treated was the difference in the size of the Kupffer cells. These cells were much larger in those patients who had not received liver than in any of those who had received liver. In the two patients showing a beginning remission, a moderate number of Kupffer's cells containing pigment was enlarged, whereas those not containing pigment appeared of normal size, except for an occasional cell that bulged into the capillary. In the patients with essentially normal blood at the time of death, the difference in the size of the Kupffer cells was more striking, for most of the cells were short and slender while only an occasional pigment-containing cell or a rare pigment-free cell appeared enlarged. The speed with which the Kupffer cells return to normal size after treatment with liver is suggested by the first two cases, since death occurred within the first eleven days of remission. This observation is of interest in connection with Peabody's<sup>13</sup> studies on the bone-marrow obtained by puncture during life. With the onset of remission he found a decrease in the number of megaloblasts, a cell supposedly arising from the "reticulo-endothelial cell" of the bone-marrow and increasing numbers of normoblasts. Some idea of the time required for the development of hypertrophy of the Kupffer cells can be gained, perhaps, from the study made of the following case.

CASE 6.—A man, in the sixth decade of life, in October, 1925, had a remission of pernicious anemia produced by liver therapy, following which the erythrocyte count remained between 4,500,000 and 5,900,000 per cubic millimeter for two years. On Oct. 11, 1927, the red blood cells numbered 5,000,000 per cubic millimeter, and the hemoglobin content was 80 per cent. Increasing symptoms and signs of a pyelonephritis caused the patient to take practically no liver after about Sept. 1, 1927. His health failed rapidly, and the number of red blood cells fell to 2,200,000 per cubic millimeter four days before his death on Nov. 12, 1927. Autopsy showed very small kidneys with chronic nephritis and pyelonephritis as the chief cause of death.

This case, therefore, is one in which relapse occurred during the month prior to death. Examination of the liver showed marked generalized hypertrophy of the Kupffer cells similar to that found in the twenty untreated patients.

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13. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, *Am. J. Path.* 3:179, 1927.

If hypertrophy of the Kupffer cells can be interpreted as indicative of increased activity, the observations given are of interest in connection with the ideas of Jungmann,<sup>14</sup> Muller<sup>15</sup> and others that the entire "reticulo-endothelial system" may be hyperactive in pernicious anemia.

Phagocytosis of red blood cells and desquamation of Kupffer's cells in the sinuses of the liver occur in pernicious anemia. The degree of this activity, however, is not in excess of that occurring in the liver in patients dying of an infectious disease, or a severe type of anemia other than pernicious anemia. It also is no greater during relapse than during remission in pernicious anemia. Phagocytic activity of the Kupffer cells may be a terminal event. This is suggested because of Peabody's<sup>16</sup> observations that phagocytosis in the bone-marrow is more evident at autopsy than in material obtained by biopsy.

Siderosis of the liver was found in both patients treated with liver and in those treated by other measures. The chief difference was one of degree. In the group not treated with liver, the pigment was found in the outer two thirds of the lobule, whereas, in the livers of the two patients who died when their blood appeared normal, the pigmentation was limited to the outer one third. This suggests that some of the pigment had been utilized in the manufacture of red blood cells, and that which remained represented the storage of pigment which had been formed in excess during relapse.

The question of blood formation in the liver in pernicious anemia is of much interest. Piney<sup>17</sup> stated that in pernicious anemia the liver is the only focus of megaloblast production, and he did not consider that this takes place in the bone-marrow. He concluded that the disease can occur only in persons who have a remnant of the megaloblastic tissue from fetal life in the liver. If this were the case, such tissue should be found during remission as well as during relapse in pernicious anemia. This observation of Piney has not been confirmed in this study. In 1905, Gulland and Goodall<sup>18</sup> examined sections of liver from seventeen cases of pernicious anemia. In eight of these they found "giant cells indistinguishable from those of the bone marrow, and the presence

14. Jungmann, P.: Ueber die Wirkungsweise der Leberdiat bei der perniziösen Anämie, *Klin. Wchnschr.* **7**:441, 1928.

15. Muller, G. L.: The Influence of Liver and Meat Diets on the Bone Marrow and the Regeneration of Red Blood Cells and Hemoglobin, *Am. J. Physiol.* **82**:269, 1927.

16. Peabody, F. W., and Broun, G. O.: Phagocytosis of Erythrocytes in the Bone Marrow with Special Reference to Pernicious Anemia, *Am. J. Path.* **1**:169, 1925. Peabody (footnote 13).

17. Piney, A.: Recent Advances in Haematology, Philadelphia, P. Blakiston's Son & Company, 1928; footnote 10.

18. Gulland, G. L., and Goodall, A.: Pernicious Anemia: A Histological Study of Seventeen Cases, *J. Path. & Bact.* **10**:125, 1905.

of large numbers of red cells, often nucleated, in the liver sinusoids." This suggested to them that in some cases parts of the liver may revert to its fetal function of blood formation. Meyer and Heineke<sup>9</sup> believed that blood formation occurred in the liver in some cases of pernicious anemia. They described the presence of mononuclear eosinophilic cells as well as a few large, protoplasm-rich, mononuclear cells, which they considered were probably neutrophilic myelocytes. Normoblasts were not found. That blood formation in pernicious anemia occurs elsewhere than in the bone-marrow is doubted by other observers. Schridde,<sup>19</sup> among other investigators, considered Meyer and Heineke's conclusions incorrectly drawn. Warthin<sup>20</sup> found no evidence of red blood cell formation in the lymphatic or hemolymphatic glands, but did not report on the liver. He believed that the presence of nucleated red cells in the sinuses could be explained by their presence in the circulating blood. The evidence from previous studies of blood formation in the liver in pernicious anemia, therefore, is not convincing. The observations recorded in this paper also give no support to such an idea, and as suggested by other investigators, it appears that the presence of megakaryoblasts in the liver of pernicious anemia is merely the result of their presence in the circulating blood.

#### SUMMARY

A contrast study was made of the histology of the livers from twenty patients with pernicious anemia not treated with liver who died during relapse, and from five patients treated with liver who died from intercurrent disease while the anemia was in partial or complete remission.

The livers from the twenty patients who died during relapse showed the following:

1. Pronounced general hypertrophy of the Kupffer cells was noted.
2. Desquamation of Kupffer's cells and phagocytosis of red blood cells were obvious, but were not more excessive than in other severe types of anemia or in infectious diseases.
3. Siderosis was marked in the liver cells and moderate in the Kupffer cells.
4. There was fatty degeneration in seven of the cases; necrosis and periportal infiltration with lymphocytes and plasma cells were present in four of these cases and also in three other cases.

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19. Schridde, H.: Ueber Regeneration des Blutes unter Normalen und Krankhaften Verhältnissen, *Centralbl. f. allg. Path. u. path. Anat.* **14**:865, 1908.

20. Warthin, A. S.: Pathology of Pernicious Anemia, with Special Reference to Changes Occurring in the Hemolymph Glands, *Am. J. M. Sc.* **124**:674, 1902.

The livers from the five patients who died in remission showed the following:

1. The Kupffer cells were of normal size, except for a relative few, which contained pigment. There was indirect evidence that this return to normal occurred within the first ten days of remission.

2. The desquamation of Kupffer's cells and the phagocytosis of red blood cells were equivalent in degree to that found during relapse.

3. Siderosis equivalent in degree to that present during a relapse was noted in cases of early remission. In the two patients whose blood appeared normal at death a slight degree of siderosis was present.

In contrast to Piney's observations, blood formation in the liver was not found in any of the twenty-five patients. Megaloblasts occurred free in the sinusoids of the liver in the patients who died during a relapse.

# HISTOLOGIC CHANGES IN THE SPLEEN IN EARLY CONGENITAL SYPHILIS

WITH SPECIAL REFERENCE TO THE ORIGIN OF ANEMIA IN THIS DISEASE \*

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The spleen in congenital syphilis has been the subject of considerable discussion throughout the literature, relatively little of which has concerned histologic change. In an exhaustive review on the pathologic anatomy of congenital syphilis presented before the German Pathological Society in 1928, Schneider<sup>1</sup> emphasized that changes in the spleen vary considerably, since the causes of its enlargement are composite, and more an indirect than a direct result of the syphilitic infection. Schneider observed that these nonsyphilitic changes include passive congestion, destruction and formation of blood and degenerative change. The more specific changes are represented by increase and thickening of reticulum, deposit of blood pigment or lipoid, vascular lesions of infiltrative or proliferative type, gummas and perisplenitis. Lubarsch,<sup>2</sup> according to Schneider, recognized three distinct types of splenic enlargement, based on histologic appearance: (1) passive congestion only, (2) proliferation of the reticulum and thickening of the trabeculae and (3) marked increase in size of malpighian corpuscles.

Considerable attention has also been given to the occurrence of severe anemias, leukemoid changes or both, with congenital syphilis. Hirschfeld<sup>3</sup> pointed out the similarity of these conditions to von Jaksch's disease (anemia pseudoleukemica or pseudoperniciosa infantum). Histologic changes in the spleen in the latter disease are usually characterized by myeloid metaplasia and pulp hyperplasia according to Naegeli<sup>4</sup>

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\* Submitted for publication, May 17, 1929.

\* From the Department of Pathology, University of Minnesota, and the Northwest Clinic, Minot, N. D.

1. Schneider, P.: Ueber die Organveränderungen bei der angeborenen Fröh-syphilis, Verhandl. d. deutsch. path. Gesellsch. **23**:177, 1928.

2. Henke, Friedrich; and Lubarsch, Otto: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1; cited by Schneider.

3. Hirschfeld, H., in Die Krankheiten des Blutes und der Blutbildenden Organe (Enzyklopaedie der klinische Medizin), Berlin, Julius Springer, 1925, vol. 1, p. 152.

4. Naegeli, O., in Die Krankheiten des Blutes und der Blutbildenden Organe (Enzyklopaedie der klinische Medizin), Berlin, Julius Springer, 1925, vol. 1, p. 9.

and Eppinger.<sup>5</sup> Schridde<sup>6</sup> observed that the same changes are often present in the spleen in congenital syphilis. Warthin<sup>7</sup> studied three instances of early congenital syphilis, showing leukemoid blood pictures, and was able to make certain that these cases were not leukemic, by virtue of marked increase of stroma and disappearance of the follicles in the spleen, changes which he considered characteristic of congenital syphilis.

Various theories have been discussed regarding the pathogenesis of anemias in congenital syphilis. Frank<sup>8</sup> divided these anemias into two groups, the one mild without other prominent characteristics, the second severe and accompanied by visceral changes, particularly splenic enlargement. Frank correlated decreasing hemoglobin and red blood cell values with increasing size of the spleen and liver, and implied that the spleen is of etiologic importance. Samberger,<sup>9</sup> however, in discussing the origin of jaundice and anemia, did not mention the spleen as a causative factor, but held the belief that the jaundice was due partly to therapeutic mercury, and partly to a syphilitic disease of the liver. French and Turner<sup>10</sup> reported a case of considerable interest in this regard, the important observations in which may be repeated briefly: A boy, aged 5 years, had had anemia since he was 9 months of age. The spleen was definitely enlarged. The Wassermann reaction was repeatedly positive. The hemoglobin content was 20 per cent; red blood cells, 1,900,000, and white blood cells, 21,000. The clinical diagnosis was: anemia pseudoleukemia infantum (von Jaksch's). Long continued antisypilitic therapy produced no benefit. Following splenectomy, without further medication, the hemoglobin content rose to 85 per cent, and apparent cure was effected.

In a recent histologic study<sup>11</sup> of seventy spleens from patients with various diseases, particular attention was given to four, three of which were from definite cases of congenital syphilis, and the fourth probably so. Changes of an unusual character were seen in these spleens, and in

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5. Eppinger, H.: *Die Hepato-Lienalen Erkrankungen*, Berlin, Julius Springer, 1920.

6. Schridde, H., in Aschoff, L.: *Pathologische Anatomie*, Jena, Gustav Fischer, 1923.

7. Warthin, A. S.: *Congenital Syphilis Simulating Leukemia and Splenic Anemia (Banti's Disease)*, *Internat. Clin.* **4**:60, 1910.

8. Frank, M.: *Zur Klinik der Anämie kongenital luetischer Säuglinge*, *Monatschr. f. Kinderh.* **31**:470, 1926.

9. Samberger: *Pathogenese der syphilitischen Anämie und des syphilitischen Ikterus*, *Arch. f. Dermat. u. Syph.* **67**:89, 1903.

10. French, H., and Turner, D.: *Case of Splenic Anemia Treated by Splenectomy*, *Proc. Roy. Soc. Med. (clinical section)* **7**:77, 1913.

11. Unpublished thesis submitted to the faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1928.



the following paragraphs these will be described, in each case preceded by a brief clinical and gross pathologic abstract.

#### CHARACTERISTIC OBSERVATIONS

CASE 1.—An infant boy, aged  $2\frac{1}{2}$  months, had respiratory difficulty at the age of 2 months. There was a moderate degree of jaundice. The liver and spleen were large. The abdominal veins were dilated. The hemoglobin content was 50 per cent; erythrocytes, 2,520,000; leukocytes, 22,000, and lymphocytes, 75 per cent. There were frequent normoblasts in blood smears, often with multiple nuclear buds. The serum bilirubin was increased (indirect van den Bergh reaction). The Wassermann reaction was positive. (The Wassermann reaction of the mother was positive also.) The weight of the spleen at necropsy was 39 Gm.

The spleen was fixed by the injection of Helly's fluid (technic described by Watson<sup>12</sup>). The sections were stained with hematoxylin and eosin, and Wright's<sup>13</sup> technic was employed for the tissue. Sections were also stained for hemosiderin, the ferricyanides and ferrocyanides of potassium with hydrochloric acid being used, and they were counterstained with hematoxylin and eosin.

The splenic sinuses were prominent, usually wide and congested; their structure was well preserved. Numerous cells were present in the sinuses, among which macrophages were frequent. Normoblasts were present in considerable number both in the sinuses and in the remaining pulp spaces. These were best recognized in the preparation stained with Wright's technic. Frequent lymphocytes and occasional polymorphonuclear leukocytes were seen. There was no evidence of myeloid metaplasia. The large free phagocytes, as well as the sinus endothelial cells, contained both red blood cells and hemosiderin more or less uniformly. Both normoblasts and mature erythrocytes were phagocytosed. The reticular cells of the pulp contained relatively small amounts of hemosiderin, and phagocytosis of red blood cells was not observed except in sinus cells. Moderate proliferation of the reticular cells of the pulp was noted.

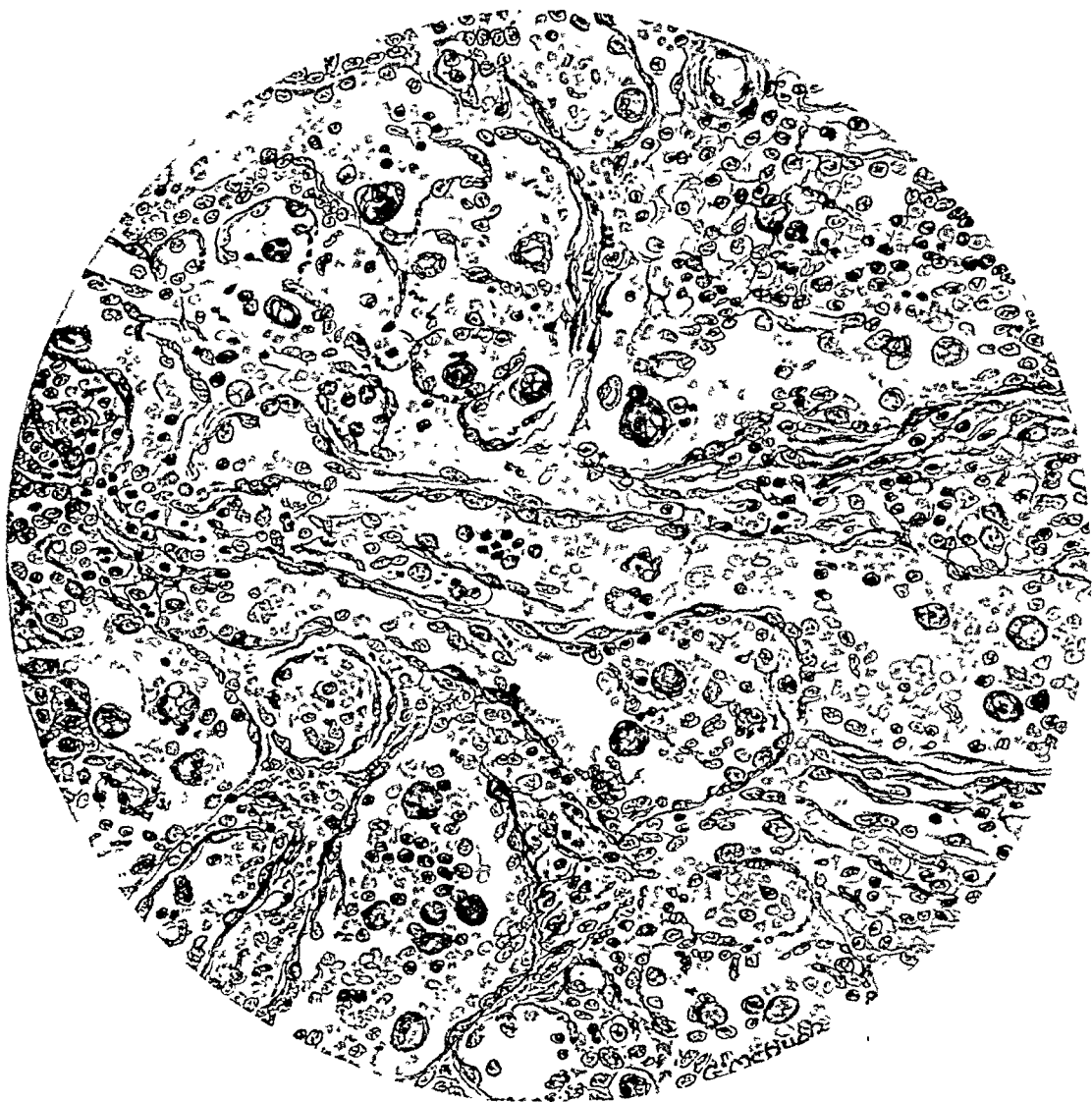
CASE 2.—An infant boy, aged  $2\frac{1}{2}$  months, took feedings poorly from birth. The symptoms included vomiting, diarrhea and fever. There was a history of general paresis in the father. Observations in the blood were first recorded shortly after an extensive accidental burn: the hemoglobin content was 44 per cent; erythrocytes, 2,890,000, and leukocytes, 72,000. Frequent immature myeloid cells were noted (leukoblasts, promyelocytes, myelocytes). There were many normoblasts. Anisocytosis, poikilocytosis, polychromasia and hypochromasia were observed. Four days following the burn the leukocytes numbered 16,000, with occasional myelocytes. The hemoglobin content was 35 per cent; erythrocytes, 2,000,000. At necropsy the organs showed no evidence of leukemia. Bilateral bronchopneumonia was present. The spleen weighed 45 Gm. There was no evidence of disease of the liver or pancreas. The epiphyses were not examined. The Levaditi stains gave negative results.

The spleen was fixed in Helly's fluid. Paraffin sections were cut at 5 microns, and stained with hematoxylin and eosin, with Wright's stain and for hemosiderin. The sinuses were prominent and fairly wide, and contained large numbers of erythrophages. There was moderate congestion of the pulp with some diffuse proliferation of the reticular cells. Many normoblasts were seen, often with mul-

12. Watson, C. J.: Histologic Variations in Diffuse Splenic Fibroses, *Folia haemat.*, to be published.

13. Wright, J. H.: Histogenesis of the Blood Platelets, *J. Morphol.* **21**:263, 1910.

tipple nuclear buds both in the sinus lumina and in the pulp spaces. Again, these were best recognized in the Wright stained sections. There was marked hemosiderosis, limited almost exclusively to the sinus macrophages. The sinus endothelial cells were also phagocytic and contained both hemosiderin and red blood cells. The latter often contained nucleated red blood cells or erythrocytes. There was no evidence of myeloid metaplasia. The lymphocytes were increased, and occasional polymorphonuclear leukocytes were observed.



Fixation by injection of Helly's fluid. Camera lucida drawing  $\times$  approximately 300 (Wright's stain). Marked erythrophagocytosis, congestion of sinuses and increase of lymphocytes. Normoblasts are difficult to recognize in the absence of color, but usually have a wider and less deeply staining cytoplasmic rim.

Congenital syphilis could only be suspected in the foregoing instance. Unfortunately, it was not possible to obtain blood from the mother for a Wassermann test. The appearance of the spleen was almost identical with that in the preceding case. The anemia undoubtedly existed prior

to the severe burn, which, however, was probably the cause of the leukemoid blood picture.

CASE 3.—An infant boy, aged 3 weeks, had a distended abdomen, a large spleen and a palpable liver. There was extreme pallor. The hemoglobin content was 24 per cent; leukocytes, 31,000, and lymphocytes, 80 per cent. The Wassermann reaction was positive. Necropsy revealed syphilitic epiphyses and intralobular cirrhosis of the liver; the spleen weighed 45 Gm. Levaditi stains were positive on various tissues.

The spleen was fixed in a diluted solution of formaldehyde U.S.P. (1:10). Paraffin sections were cut at 7 microns and stained with hematoxylin and eosin, and for hemosiderin. There was moderate congestion of the pulp spaces. The sinuses were prominent, and contained numerous macrophages, as well as lymphocytes, and red blood cells. The large phagocytes contained both erythrocytes and large amounts of hemosiderin. Little was present elsewhere. Normoblasts were frequently observed, both free and in phagocytes. There was moderate proliferation of the reticular cells of the pulp.

CASE 4.—An infant girl, aged 8 weeks, had a papular eruption over the skin, rhagades about the mouth and splenomegaly. Results of examinations of the blood were not recorded. There was temporary improvement after syphilitic therapy.

Necropsy revealed syphilitic osteochondritis and interstitial pancreatitis. The spleen weighed 76 Gm.

The spleen was fixed in a diluted solution of formaldehyde U.S.P. (1:10). Paraffin sections were cut at 7 microns and stained with hematoxylin and eosin, and for hemosiderin.

There was moderate diffuse proliferation of the reticular cells of the pulp. The sinuses were prominent and contained frequent clumps of free cells, including lymphocytes, red blood cells and macrophages. The latter contained both erythrocytes and hemosiderin. Free sinus endothelial cells were also noted. Normoblasts were of frequent occurrence both in the pulp spaces and in the lumina of the sinuses. Hemosiderin was not increased to the extent observed in the three previous instances, although it was present in considerable amount, largely in phagocytes, and to a lesser extent in the pulp spaces.

#### COMMENT

Although destruction of the blood has been mentioned in the literature as one of the nonsyphilitic changes occurring in the spleen in congenital syphilis, I have not found any description of such marked erythrophagocytosis and hemosiderosis as were observed in the instances reported here. No emphasis has been placed on the occurrence of such changes, nor on their relationship to the severe anemias which are commonly present in congenital syphilis.

The histologic appearance varied but slightly in each of the four spleens described. Numerous macrophages were characteristic, containing both nucleated and mature red blood cells and large amounts of hemosiderin. The phagocytes were almost wholly in the sinuses; attached sinus endothelial cells were also phagocytic. Normoblasts were of frequent occurrence. Evidence was lacking to prove that these were of local origin, and other signs of myeloid metaplasia were absent.

In three of the foregoing instances severe anemias were prominent during life; the characteristics of the blood were not recorded in the fourth. In one of the three patients with anemia, syphilis was not proved to be present although it was strongly suggested. In both instances in which the blood picture was studied, the anemia was of a definitely regenerative type, while in one bilirubinemia was present, and the van den Bergh reaction was indirect. These observations, together with the histologic changes in the spleens as described, constitute evidence that the anemias were hemolytic, and imply that the spleen plays an important rôle in their origin.

#### CONCLUSION

Extensive destruction of the blood may occur in the spleen in congenital syphilis, and is probably an important factor in the production of anemia. Marked erythrophagocytosis and hemosiderosis is observed as evidence of this destruction. The macrophages are largely of sinus endothelial origin, and fixed sinus endothelial cells are also phagocytic.

# THE EFFECT OF ALUMINUM ON MAMMALIAN BLOOD AND TISSUES \*

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There is comparatively little to be found in the literature concerning the effects of alum on the mammalian organism, when administered either in large doses or in small doses for long periods. We have therefore undertaken a series of experiments to secure information concerning the toxic effects of aluminum, especially in the form of alum (sodium aluminum sulphate). Two methods of attack were used. In the first, aluminum compounds were injected intravenously, and the effects on the blood cells, on the formation of antibodies and on the tissues were noted. These experiments demonstrated that markedly toxic effects resulted when the aluminum ion was put directly in contact with body tissues. To learn whether aluminum administered by mouth can be absorbed sufficiently to produce similar effects, aluminum compounds were fed in small doses over an extended period of time, and finally large single doses were fed at one time. When effects followed ingestion of the aluminum compounds similar to those caused by direct injection, the conclusion seemed warranted that the aluminum ion is able to pass through the alimentary tract and is then able to do damage to the tissues.

It has been contended that aluminum, as it is commonly eaten in the largest amounts, that is, in the form of food prepared with alum baking powder, is in an insoluble form which resists absorption and passes on through the alimentary tract as inert material. Evidence, however, has been brought to light showing that this may not be altogether the case. Steel,<sup>1</sup> in 1911, showed that aluminum in alum baking powders was not rendered wholly insoluble in the baking process and that it was found in the blood of dogs that ate biscuits made with the powder. Kahn<sup>2</sup> also showed that aluminum was absorbed into the blood stream after ingestion of aluminized biscuits. Much was eliminated in the urine and feces, but a considerable amount was distributed in the various tissues of the body. Aluminum was found by

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\* Submitted for publication, April 16, 1929.

\* From the Otho S. A. Sprague Memorial Institute and the Department of Pathology of the University of Chicago.

1. Steel, M.: *Am. J. Physiol.* **28**:94, 1911.

2. Kahn, Max: *Biochem. Bull.* **1**:235, 1911-1912.

Balls<sup>3</sup> in the blood of men fed aluminized biscuits. Evidence was submitted by Myers and Killian<sup>4</sup> that from 2 to 20 per cent of the aluminum compounds ingested in baking powder residues was found in soluble form and a smaller proportion in solution in the gastric contents of eighteen subjects. Somewhat similar observations were made on the solubility of aluminum in the duodenal contents of four subjects.

The French investigators Schaeffer, Fontés, LeBreton, Oberling and Thivolle<sup>5</sup> recently found that aluminum phosphate, as it is found in some baking powders, is soluble both in vitro and in vivo in the hydrochloric acid of the gastric juice. Furthermore, it is not reprecipitated in the duodenum by the alkaline pancreatic juice when the chyme is neutralized. Bile prevents this (precipitation) in an as yet undetermined manner.

Mull, Morrison and Myers,<sup>6</sup> using the aurin reaction of Hammett and Sottery,<sup>7</sup> reported finding less than 0.2 mg. aluminum per hundred cubic centimeters in the blood of thirteen hospital patients with miscellaneous diseases and in pig's blood. Recently Myers, Mull and Morrison<sup>8</sup> reported the aluminum content of rat liver, per hundred grams, to be: 0.130 mg. in control rats; 0.161 mg. in rats fed aluminum; 0.063 mg. in rats fed an aluminum-free diet, and 8.2 mg. in rats receiving intraperitoneal injections of aluminum. They found the aluminum content of dog liver per hundred grams, to be 0.150 mg. in control dogs and 0.266 mg. in dogs receiving aluminum. In the autopsy material from man they found the following amounts of aluminum per hundred grams of tissue: in the heart, 0.225 mg.; in the brain, 0.203 mg.; in the liver, 0.074 mg, and in the gallbladder with bile, 0.069 mg. From their data, they concluded<sup>9</sup> that traces of aluminum are present in the tissues normally and that the amount is slightly increased on a diet containing considerable aluminum. The growth curves of animals receiving aluminum, however, compare well with those of the controls, the only difference being that the rats fed aluminum showed a slightly greater initial growth. They further concluded<sup>10</sup> that when aluminum compounds are administered orally to dogs, the absorption of the aluminum is slight.

3. Balls, A. K.: Dissertation, Columbia University, New York.

4. Myers, V. C., and Killian, J. A.: *J. Biol. Chem.* **78**:591, 1928.

5. Schaeffer, G.; Fontés, G.; LeBreton, E.; Oberling, C., and Thivolle, L.: *Bull. Soc. d'hyg. aliment.* **16**:1 and 49, 1928.

6. Mull, J. W.; Morrison, D. B., and Myers, V. C.: *Proc. Soc. Exper. Biol. & Med.* **27**:476, 1927; *J. Biol. Chem.* **78**:595, 1928.

7. Hammett, L., and Sottery, C. T.: *J. Am. Chem. Soc.* **47**:142, 1925.

8. Myers, V. C.; Mull, J. W., and Morrison, D. B.: *J. Biol. Chem.* **78**:595, 1928.

9. Myers, V. C., and Mull, J. W.: *J. Biol. Chem.* **78**:605, 1928.

10. Myers, V. C., and Morrison, D. B.: *J. Biol. Chem.*, **78**:615, 1928.

There have been numerous claims that aluminum is not absorbed into the blood stream following oral ingestion, such as the report by Taylor.<sup>11</sup> In a recent study, McCollum, Rask and Becker,<sup>12</sup> with the use of a spectroscopic method for determining aluminum, were unable to demonstrate that aluminum is a constituent of either plant or animal matter, and stated that compounds of this element are not absorbed out of the stomach or intestinal tract when present in the diet. This is not in agreement with the results of Mull, Morrison and Myers and others and can scarcely be accepted until repeated and confirmed.

### EFFECTS OF INTRAVENOUS INJECTIONS OF ALUMINUM

Rabbits were used in all the experiments. The effects of aluminum on the number of red and white blood corpuscles, on the relative proportions of the different leukocytes, on the fragility or the resistance of the red cells to hemolysis with saponin and hypotonic salt, on the percentage of hemoglobin, on the body weight and on the histology of the various tissues, as well as the clinical symptoms, were noted.

The investigations in this part, dealing with intravenous injections of aluminum compounds, were divided into two types of experimentation: One dealt with the effects following intravenous injection of small daily doses of different aluminum compounds over an extended period of time. The other dealt with the effects following intravenous injection of a single large dose or a few large doses, in order that we might determine the amount of sodium aluminum sulphate that can be tolerated at one time.

### TECHNIC

The red cell count and the total and differential leukocyte counts were made in the usual manner in a Levy counting chamber, before any injections were given and at frequent intervals thereafter. These counts were made before the rabbits were fed their daily ration. Two counts were made in every case reported in this paper and the average recorded. No numbers were accepted that varied more than from 300,000 to 500,000 erythrocytes or 1,000 leukocytes. The percentage of hemoglobin was determined by the Sahli method, and the fragility of the corpuscles was studied by determining the degree of hemolysis with saponin and hypotonic salt solutions.

The hemolytic methods used were those described by Bigland,<sup>13</sup> with modifications. For example, a series of six tubes was set up, containing the following amounts of 0.8 per cent sodium chloride: 1.4, 1.5, 1.6, 1.7, 1.8 and 1.9 cc. Then 1 cc. of a 1 per cent solution of sheep's blood made in saline solution was added to each tube. And, lastly, the following amounts of a 0.01 per cent saponin saline

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11. Taylor, A. E.: *Alum in Foods*, Bull. 103, U. S. Dept. of Agric., 1914.

12. McCollum, E. V.; Rask, O. S., and Becker, J. E.: *J. Biol. Chem.* **77**:753, 1928.

13. Bigland, A. D.: *Quart. J. Med.* **7**:369, 1914.

solution were added: 0.6, 0.5, 0.4, 0.3, 0.2 and 0.1 cc., making a total of 3 cc. in each tube. Each tube was shaken well and allowed to stand at 37.5 C. for two hours and then over night at room temperature. The following day, the amount of hemolysis was read by noting the last tube in which complete hemolysis had occurred. By comparing, in this manner, the number of cubic centimeters of a standard saponin solution required to hemolyze completely a definite amount of blood of a rabbit before treatment, with the amount required after treatment, it was possible to determine whether the fragility of the blood cells was increased or decreased. It was found that the weaker (1 per cent) solution gave more clearcut readings than did a stronger (5 per cent) solution, and still the absolute values obtained in the two cases were identical.

The determination of the fragility of the red cells by means of the hypotonic salt solution was similar in process. A series of nine tubes was set up containing the following amounts of physiologic solution of sodium chloride: 1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8 and 2 cc. To each was added 1 cc. of a 1 per cent solution of whole blood made with saline solution, and then distilled water sufficient to make a volume of 3 cc. The resulting percentage of saline, which was just sufficient to produce complete hemolysis, could be easily calculated and was reported accordingly.

At first, an attempt was made to determine the hemolysis of blood cells washed free from serum, but the excessive bleeding that was necessary to secure adequate amounts for this determination had deleterious effects on the rabbits and greatly complicated the results due to the aluminum solutions. Hence this test was eliminated. The few preliminary experiments performed, however, showed that washed blood cells of normal rabbits are slightly less resistant to hemolysis by saponin than are the blood cells when mixed with their normal serum, a result which confirms the work of M'Neil.<sup>14</sup> There seemed to be no difference in hemolysis with hypotonic salt solution between washed and unwashed cells.

#### INTRAVENOUS INJECTIONS OF SMALL DAILY DOSES

Rabbits were each given a daily intravenous injection of from 5 to 10 cc. of an aluminum solution containing an amount of aluminum which would be comparable with the amount found by Kahn in the blood stream of dogs that had been fed aluminized biscuits. For example, he found an average of 1.7 mg. of aluminum, determined as  $\text{Al}_2\text{O}_3$ , per hundred grams of blood in three dogs fed aluminized biscuits for from fifty-five to sixty days. Calculated for an average rabbit weighing 3 kg., the daily injection of 0.04 Gm. of sodium aluminum sulphate ( $\text{Al}_2[\text{SO}_4]_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ ) or 0.01 Gm. of aluminum chloride ( $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ ) would constitute a comparable amount of aluminum ion in the blood stream.

Both of these solutions were acid: the 0.8 per cent solution of  $\text{Al}_2(\text{SO}_4)_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$  having a  $p_H$  of 3.4 and the 0.2 per cent solution of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  Having a  $p_H$  of 3.8. Since acid is known to hemolyze blood cells, it was thought that the anemia produced by the

14. M'Neil, C.: J. Path. & Bact. **15**:56, 1910-1911.



injection of these aluminum solutions might possibly be due to the hydrogen ion concentration of the solutions. Sulphuric acid, therefore, of such strength that its  $p_H$  was 3.4, was injected intravenously into two rabbits for the same length of time as the aluminum solutions. Moreover, since sodium aluminum sulphate solutions liberate their acid slowly, a  $p_H$  determination does not indicate the amount of acid that is capable of being released, and therefore, a sulphuric acid solution of acidity corresponding to the maximal amount of acidity that could be liberated by the corresponding aluminum solution, namely, a  $p_H$  of 2.6, was also injected daily into two rabbits. It is not probable, however, that the tissues were ever subjected to such a high degree of acidity at any one time from the alum injected, for all of the acid would probably not have been released instantaneously, and the buffering action of the blood would have considerably diminished the acidity.

*Results with  $Al_2(SO_4)_3 \cdot Na_2SO_4 \cdot 24H_2O$ .*—Five rabbits, no. 1 (3.6 Kg.), no. 2 (3.4 Kg.), no. 10 (2.4 Kg.), no. 15 (2.7 Kg.) and no. 20 (2.5 Kg.), which were given intravenous injections of 0.04 Gm. each of sodium aluminum sulphate ( $Al_2[SO_4]_3 \cdot Na_2SO_4 \cdot 24H_2O$ ) daily, all developed a secondary anemia after a period of from eleven to twenty days (chart 1). The percentage of hemoglobin always decreased considerably. The number of red cells per cubic centimeter showed an ultimate decline in every rabbit, except no. 15, extending as low as 1,870,000 in no. 1. The total number of leukocytes per cubic centimeter usually rose, reaching its peak, as high as 25,650, in rabbit 10, about the time that the number of erythrocytes per cubic centimeter was the lowest, and the increase was usually in the number of small mononuclear lymphocytes (chart 2). In order to save space the polymorphonuclear and mononuclear leukocyte curves for all five rabbits have been superimposed on each other and from these a single average curve computed and recorded.

The blood cells became more resistant to hemolysis as treatment continued (chart 3). In other words, a more hypotonic saline solution was required to hemolyze the cells, after treatment of the rabbit with aluminum compounds. This increased resistance of the blood cells to hemolytic agents was also demonstrated (to a slight extent) with saponin, for more saponin was necessary to hemolyze the blood at the end of the experiment than in the beginning.

A study of the blood cell picture (Wright's stain) revealed in all five rabbits a marked development of abnormal cells, similar to those found in lead poisoning. Some nucleated erythrocytes or normoblasts were always found in the later stages. Polychromasia, poikilocytosis and anisocytosis were marked. Stippled cells were found.

In addition to these definite indications of anemia, all five rabbits showed unmistakable symptoms of local aluminum poisoning. The

ears into the veins of which the aluminum solution was injected became edematous, inflamed and then necrotic, so much so that portions of the ears of some of the rabbits sloughed off. This, of course, was due to the irritant effects of the aluminum on the tissue or to thrombosis of the vessels, and was undoubtedly a local reaction. Swellings later

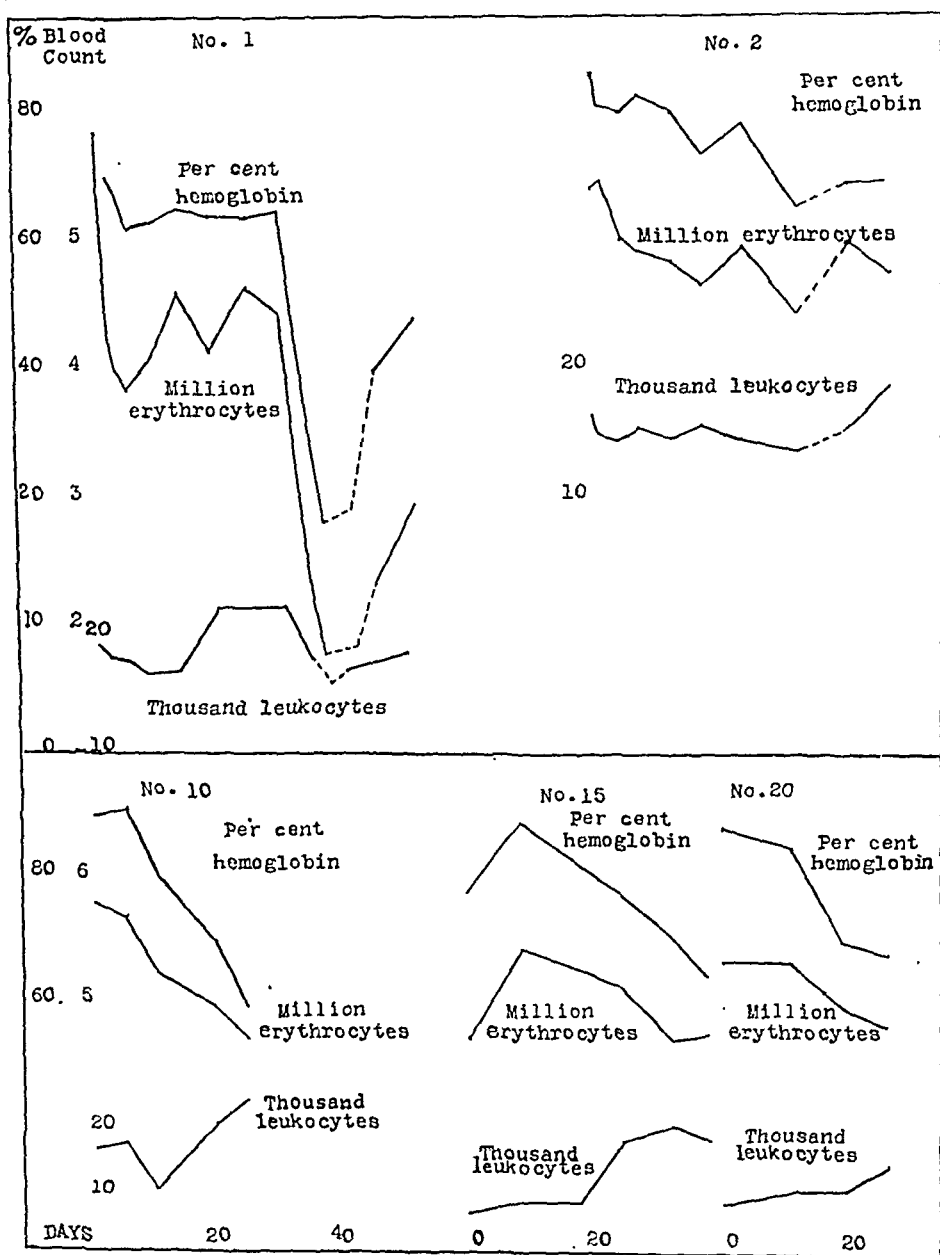


Chart 1.—The individual hemoglobin, erythrocyte and leukocyte curves of five rabbits following daily intravenous injection of 0.04 Gm. each of sodium aluminum sulphate.

appeared on the under side and the back of the neck and in the axillary glands in all five rabbits. The rabbits, as a whole, lost comparatively little weight, in spite of the development of roughened hair and a sickly

appearance. However, no. 1 lost  $1\frac{3}{8}$  pounds (1.2 Kg.) and gave the most marked reactions of all. The temperatures of nos. 1 and 2 never rose much above normal, while that of no. 10 reached 105.6 F. three days before its death, which was probably due to sepsis.

The toxic effects of injecting aluminum solutions are not surprising when the effects of aluminum on the blood in vitro are seen. When a

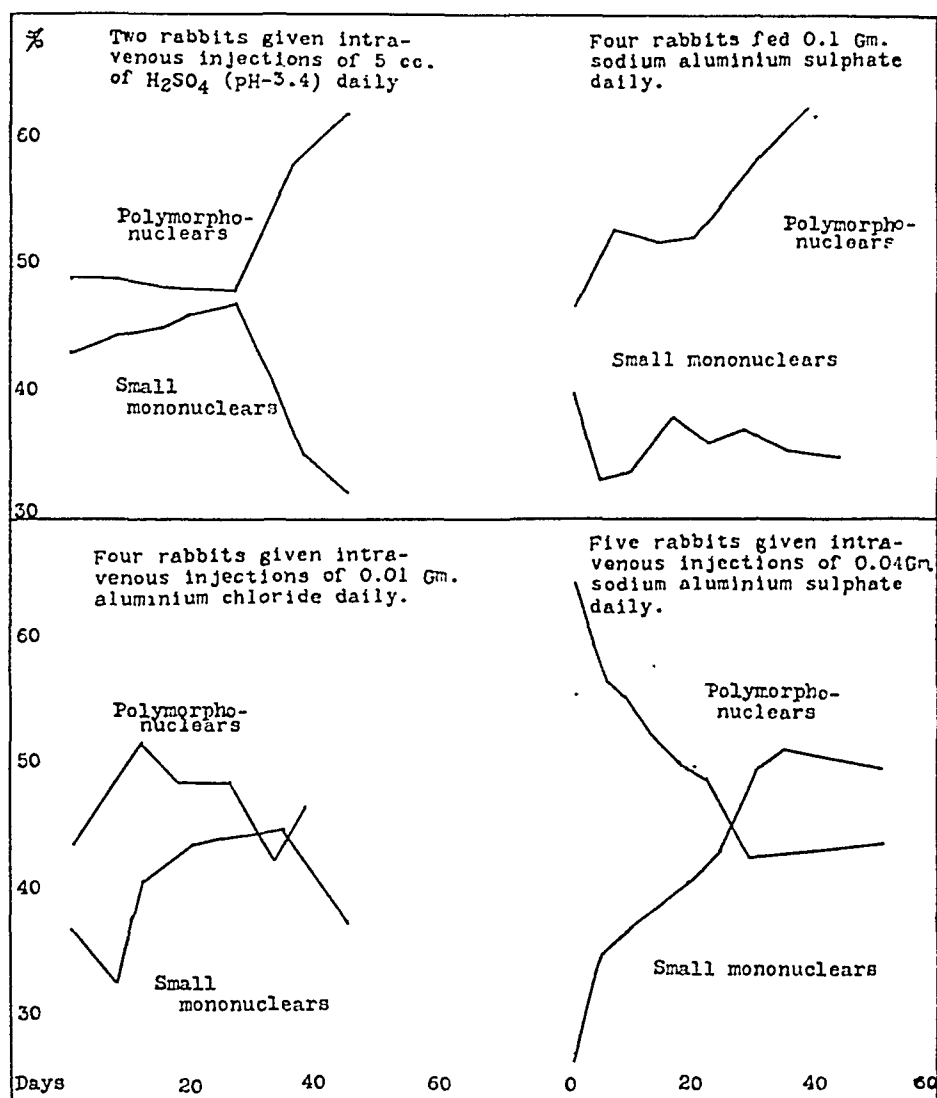


Chart 2.—The average leukocyte curves of rabbits following daily intravenous injection of sulphuric acid; daily intravenous injection of aluminum chloride; daily intravenous injection of sodium aluminum sulphate, and daily oral ingestion of sodium aluminum sulphate.

drop of fresh blood of a normal rabbit was placed in a small amount of a solution of sodium aluminum sulphate of the strength used for injections, almost immediately the hemoglobin was expelled from the corpuscles and decomposed to a brown hematin solution, and a white,

flocculent precipitate formed. When the blood was dropped into the solution of aluminum chloride, a clear brown hematin solution resulted. But when the blood was dropped into a sulphuric acid solution of a  $p_H$  of 3.4, no hemolysis occurred; in fact, the cells became closely packed in the bottom of the tube and remained there for days unhemolyzed.

*Results with  $AlCl_3 \cdot 6H_2O$ .*—Four rabbits, no. 3 (2.7 Kg.), no. 9 (2.9 Kg.), no. 12 (2.7 Kg.) and no. 14 (2.4 Kg.), received intravenous

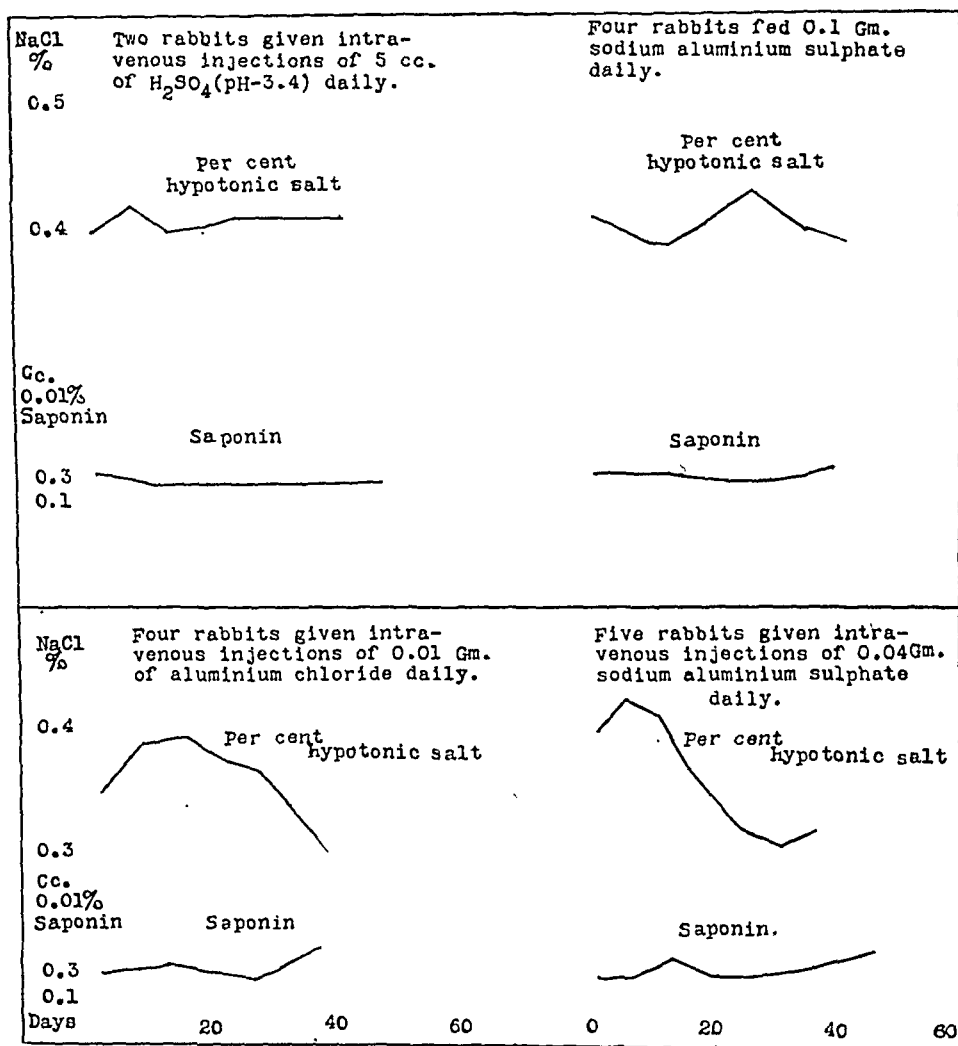


Chart 3.—The average curves for the hemolysis of red cells by hypotonic salt and saponin in rabbits treated with aluminum compounds (controlled by the curves of two treated with sulphuric acid).

injections of 0.01 Gm. each of aluminum chloride ( $AlCl_3 \cdot 6H_2O$ ) daily (chart 4). In every rabbit there was a marked decrease in homoglobin. In all but one, the resistance to hemolysis increased in the later stages (chart 3). The number of erythrocytes fell somewhat in all except no. 12. At certain times, all showed a definite leukocytosis, and in nos. 3, 12 and 14 the increase seemed to be in the number of the small

mononuclear lymphocytes (chart 2.) Abnormal blood cells, chromatophilic cells, poikilocytes, anisocytes and normoblasts were found in the later stages, as in the blood of rabbits treated with sodium aluminum sulphate ( $\text{Al}_2[\text{SO}_4]_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ ). The experiment on rabbit 9 was discontinued sooner than usual because of the development of an

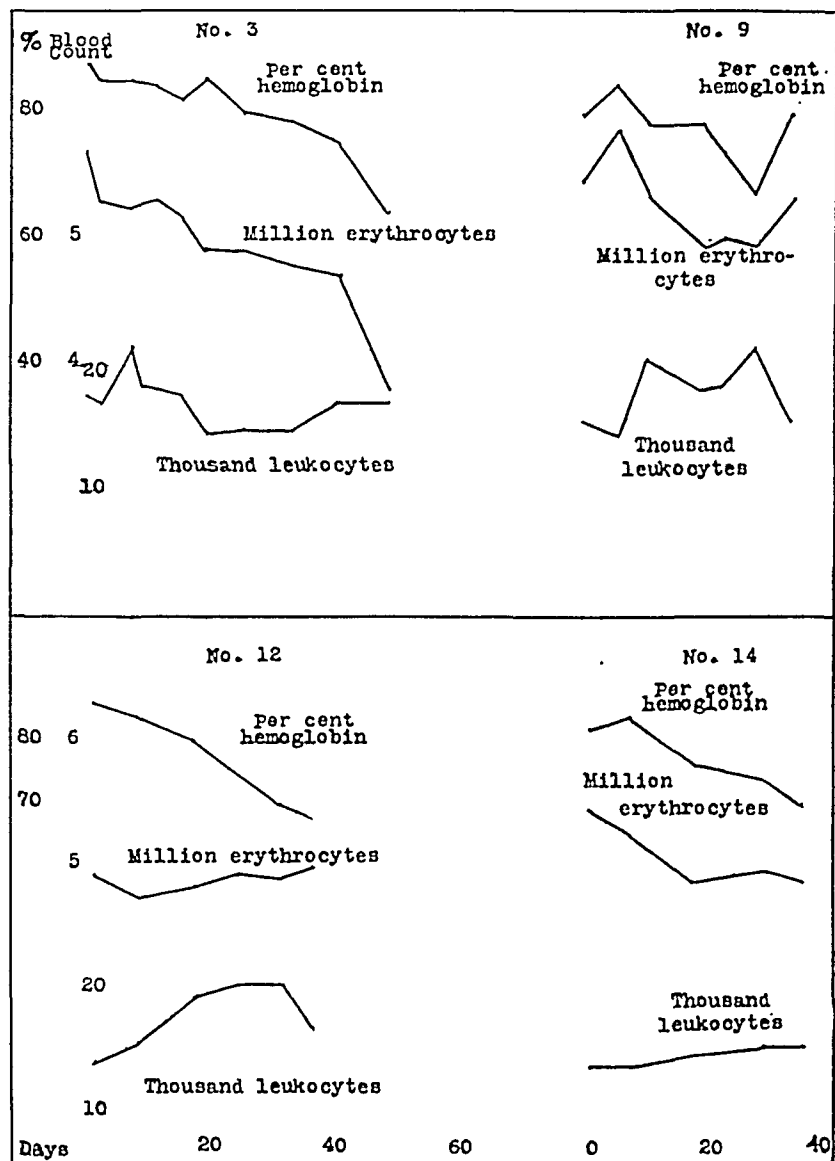


Chart 4.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits following daily intravenous injection of 0.01 Gm. each of aluminum chloride.

infection in the inner ear. In all four rabbits, swelling, edema, inflammation and necrosis of the ears appeared as soon and almost to the same extent as in rabbits treated with sodium aluminum sulphate. Nos. 3 and 12 in the later stages displayed swellings on the under side and

on the back of the neck. There was practically no loss of weight in any of the rabbits, but all became quiet and sickly.

*Results of Control Injections of Acid Solutions.*—Two rabbits, no. 5 (3.6 Kg.) and no. 11 (3 Kg.), for forty-five and thirty-six days, respectively, received daily intravenous injections of 5 cc. each of a sulphuric

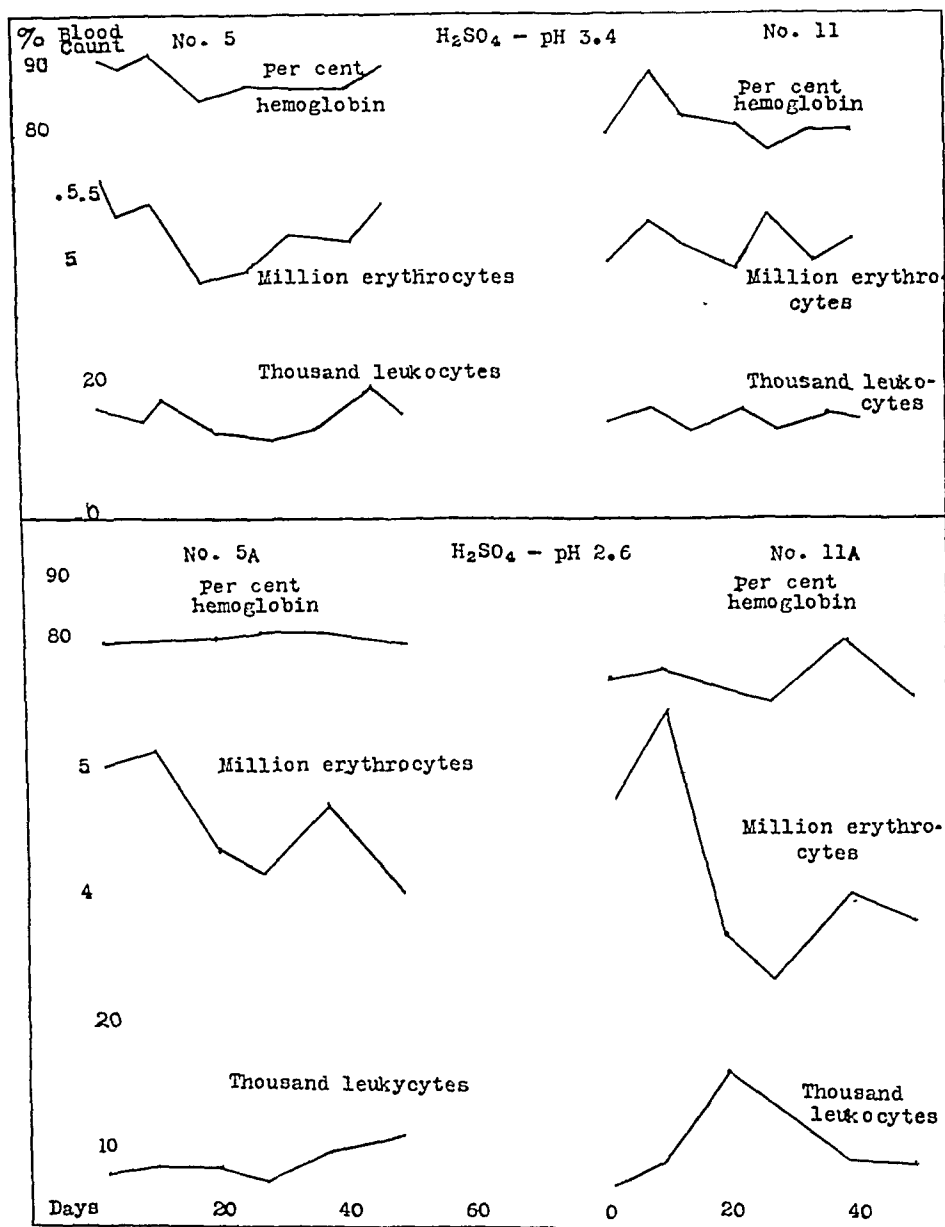


Chart 5.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits following daily intravenous injection of 5 cc. each of sulphuric acid.

acid solution of such strength that its  $p_H$  was 3.4. As indicated before, this was found to be the  $p_H$  of the 0.8 per cent solution of sodium aluminum sulphate injected (chart 5). At the end of and during these periods both rabbits appeared sleek and in perfect health and did not show any

of the marked symptoms or blood pictures described as occurring in the former groups of experiments.

Since more acid is liberated from sodium aluminum sulphate when it comes in contact with tissue than is free in the original solution, it is possible that some of the harmful effects reported following injections of the aluminum solution may be due to the acid liberated after the solution was injected. Therefore, sulphuric acid solution with a  $p_H$  of 2.6, which corresponds to the maximal amount of acid which can be liberated by the sodium aluminum sulphate, was injected intravenously daily into two rabbits, 5A (2.7 Kg.) and 11A (2.7 Kg.), for forty-nine days (chart 5). It is improbable, however, that this amount of acid would ever be free in the blood stream at any one time following injection of sodium aluminum sulphate solution because of the buffering capacity of the blood. There was no decrease in the percentage of hemoglobin, and there were no abnormal blood cells, but the total number of red cells did decrease. For a while during the experiment, the ear of one rabbit (11A) became swollen, owing to the irritant effects of the solution injected, and during this time the number of leukocytes rose. The other rabbit was in perfect health throughout the experiment and showed none of these symptoms.

#### THE LETHAL DOSE OF SODIUM ALUMINUM SULPHATE

Since the five rabbits that had received injections of sodium aluminum sulphate were able to tolerate for a considerable length of time daily doses of about 5 cc. containing 0.04 Gm. of the salt in 0.8 per cent concentration, it seemed of interest to determine what amount of the compound given in this way was lethal and in what concentration. Therefore, one rabbit (1.8 Kg.) was given an intravenous injection of 10 cc. of a solution containing 0.25 Gm. of sodium aluminum sulphate in 2.5 per cent concentration. Immediately, the rabbit's back bowed, and it cried, became limp, stopped breathing and died in spasms.

Another rabbit (1.8 Kg.) was then given an injection of the same total amount (0.25 Gm.) of sodium aluminum sulphate, but this time the salt was given in a large volume of solution or a weaker concentration, namely, 32.5 cc. of solution of 0.8 per cent strength. The rabbit trembled during the injection of the last 10 cc., but soon recovered completely. Three days later the rabbit was given 0.32 Gm. in 40 cc. in the same concentration over a period of two hours and the following day 0.16 Gm. in 20 cc. The rabbit did not collapse, but from then on it seemed to decline and became more quiet than normal, and its coat was roughened. Twenty-four days later it was found dead, having received a total of 0.73 Gm. in 72.5 cc. of a solution of a concentration of 0.8 per cent. At autopsy, petechiae were found in the mucosa of the stomach. The intestinal mucosa was red and microscopically showed

small areas of necrosis and mitosis in numerous epithelial cells. The spleen was small and fibrous, and microscopically it showed fibrosis and extensive necrosis of the pulp.

A third rabbit (1.6 Kg.) was given an intravenous injection of 10 cc. of 0.8 per cent solution (or 0.08 Gm.). Immediately, it showed slight symptoms of collapse. Eleven days later, it received the same dose and manifested no symptoms. Four days after this, it received five injections of 10 cc. each of a 1 per cent solution at hourly intervals and still showed no symptoms. The following morning, immediately after a single injection of 10 cc. of a 1 per cent solution, it died. This rabbit therefore died after receiving a total of 0.76 Gm. of the aluminum compound. At autopsy, extensive necrosis was found in the splenic pulp and some spontaneous nephritis, but no abnormalities of the alimentary tract.

Therefore, it can be stated approximately that a rabbit weighing 1.5 Kg. will survive an intravenous injection of 0.7 Gm. of sodium aluminum sulphate, if given in an 0.8 to 1 per cent concentration, but will be killed by any amount over this, given in a short period of time. And if the salt is more concentrated, the rabbit will not tolerate nearly so large an amount. However, small daily doses (5 cc.) of a solution of 0.8 per cent can be tolerated up to sixty days and longer, or until, as was the case in several of the rabbits receiving the injections, the rabbit is moribund and no longer offers a superficial vein for injection because of the necrotizing effect of the solution of aluminum on the surrounding tissues.

#### ANATOMIC STUDY OF THE RABBITS FED OR GIVEN INJECTIONS OF SMALL DOSES OF ALUMINUM

A careful study of the anatomic changes in the rabbits given injections of sodium aluminum sulphate and aluminum chloride, as compared with the control animals (those given injections of sulphuric acid solutions of corresponding acidity or fed lactose), revealed only one type of injury as certainly due primarily to the treatment, namely, pigmentation, thrombosis, necrosis and fibrosis in the spleen. On the whole, the spleens of the rabbits fed or given injections of the aluminum compounds were more heavily pigmented than were the spleens from the control rabbits given injections of sulphuric acid. However, later study of the spleens from rabbits fed only lactose and considered as normal revealed considerable pigmentation in three of four cases. It is true that necrosis of the splenic pulp cells was found only in the rabbits receiving injections of the solution of sodium aluminum sulphate, and this was extremely marked in several of these animals. The fact that there was such marked necrosis in the splenic pulp in the animals receiving large doses of alum, and that pigmentation and fibrosis were found so frequently



in the other animals, suggests the probability that the hemagglutinative effect of aluminum may be responsible for these changes in the spleen.

Some of the alimentary changes, such as petechiae and ulcers of the stomach and intestinal mucosa, probably had some relation to the treatments with alum, since they were found chiefly in those rabbits fed aluminum or given injections of it, even though they were not found constantly. This view is supported by the fact that similar intestinal lesions were found in mice fed alum by Schaeffer, Fontés LeBreton, Oberling and Thivolle.<sup>5</sup>

Focal necrosis of the liver cells seemed to be associated chiefly with infections, for example, bronchitis and pneumonia, and therefore it was found chiefly in the rabbits that had died of infections and cannot be attributed to the alum.

In summing up the microscopic study of the tissues of the twenty-six rabbits used in these experiments, it can be said that many of the pathologic lesions are not necessarily to be accredited to the treatment with aluminum compounds, since so many similar abnormalities were found in supposedly normal rabbits. The severe lesions in the spleens, however, for instance, the fibrosis and the necrosis, of even those rabbits receiving small daily doses of alum were probably due to the treatment with aluminum. The marked changes (to be described later) in the kidneys of the rabbits fed large doses of aluminum compounds and the extensive vacuolization and granular degeneration of renal epithelium in the rabbits fed small daily doses or given intravenous injections of sodium aluminum sulphate for a long period of time were not to be found in any of the control rabbits and were therefore, presumably, truly an aluminum effect. The agglutination thrombi found in the lungs, liver and kidneys of some of the animals were also never observed in the control rabbits.

## EFFECTS OF FEEDING OF ALUMINUM

The experiments in this part deal with the effects following the feeding of small daily doses of sodium aluminum sulphate to rabbits over short periods (two months) and over long periods (up to one year); and the effects following the feeding of a single large dose or a few large doses of different aluminum compounds.

### FEEDING OF SMALL DAILY AMOUNTS

Eight rabbits, nos. 8 (4.07 Kg.), 16 (3.2 Kg.), 17 (2.5 Kg.), 35 (2.5 Kg.), 36 (2.5 Kg.), 37 (2.7 Kg.), 61 (2.8 Kg.) and 500 (4.07 Kg.), were each fed daily a gelatin capsule containing 0.1 Gm. of sodium aluminum sulphate ( $\text{Al}_2[\text{SO}_4]_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ ) mixed with powdered lactose. This amount of the salt fed to a rabbit weighing 4 Kg. is comparable with the amount fed by Kahn to dogs. For example,

he fed 15 Gm. of aluminized biscuit per kilogram, and his analyses show that this amount of biscuit contains 2.4 mg. of  $\text{Al}_2\text{O}_3$ , which is equivalent to 21.53 mg. of sodium aluminum sulphate ( $\text{Al}_2[\text{SO}_4]_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ ). In the case of four rabbits, the feeding was continued for only a short period, up to sixty days, and in the case of four others the feeding lasted from 150 to 350 days. In all except Nos. 35 and 37 (charts 6 and 7) the percentage of the hemoglobin

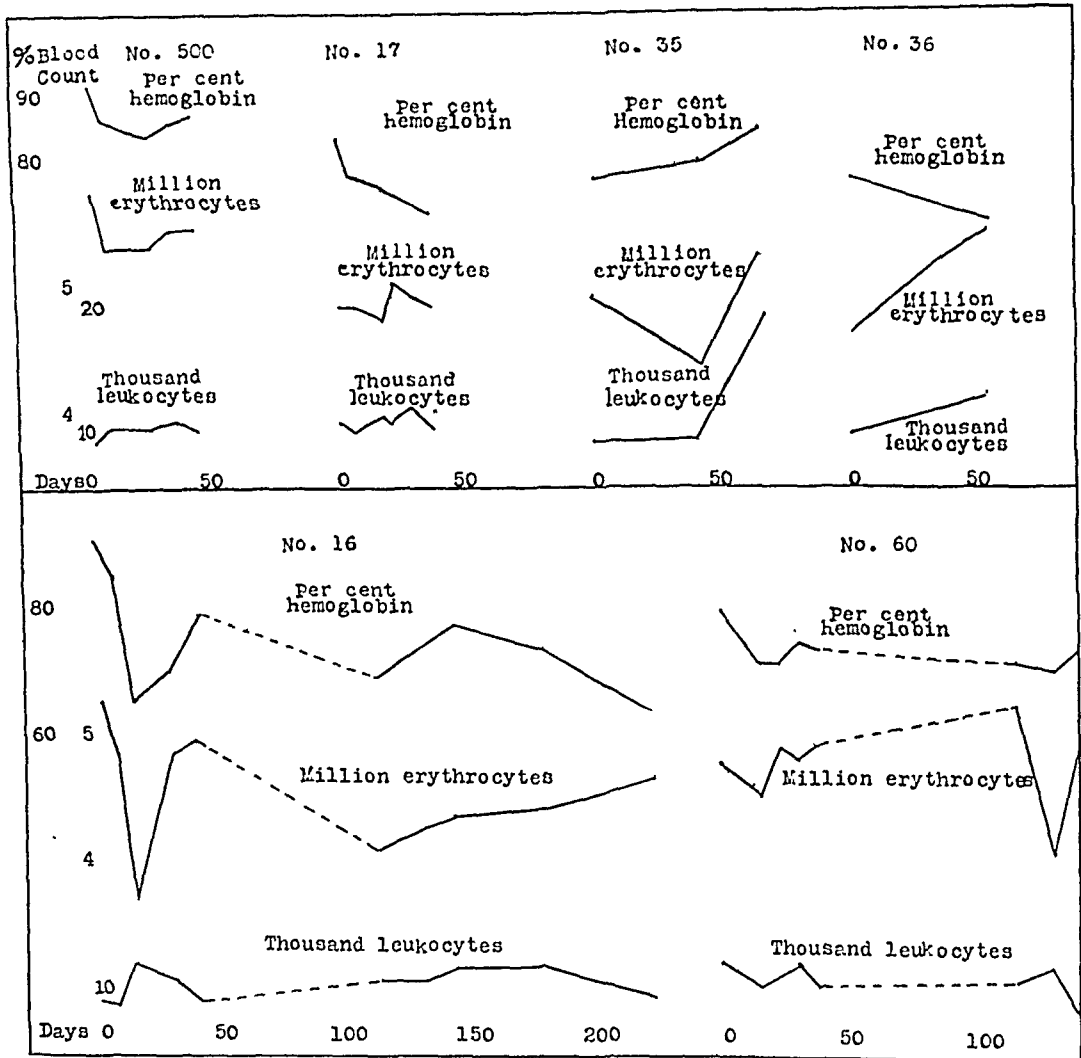


Chart 6.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits fed daily 0.1 Gm. each of sodium aluminum sulphate. The dotted line represents a period during which the feeding of the aluminum salt was suspended.

decreased, during the experiment, more than in the control rabbits (chart 8) fed only lactose. These two rabbits, nos. 35 and 37, as well as no. 36, showed a decided increase in the number of erythrocytes, comparable to that in the control rabbits fed lactose. An explanation

of this phenomenon is wanting. It is noteworthy that in many of the alum-fed rabbits, especially rabbits 35, 16, 60 and 8, periods of marked depression of the number of erythrocytes are followed by periods of a rise in their number. There was practically no change in the total number of the leukocytes.

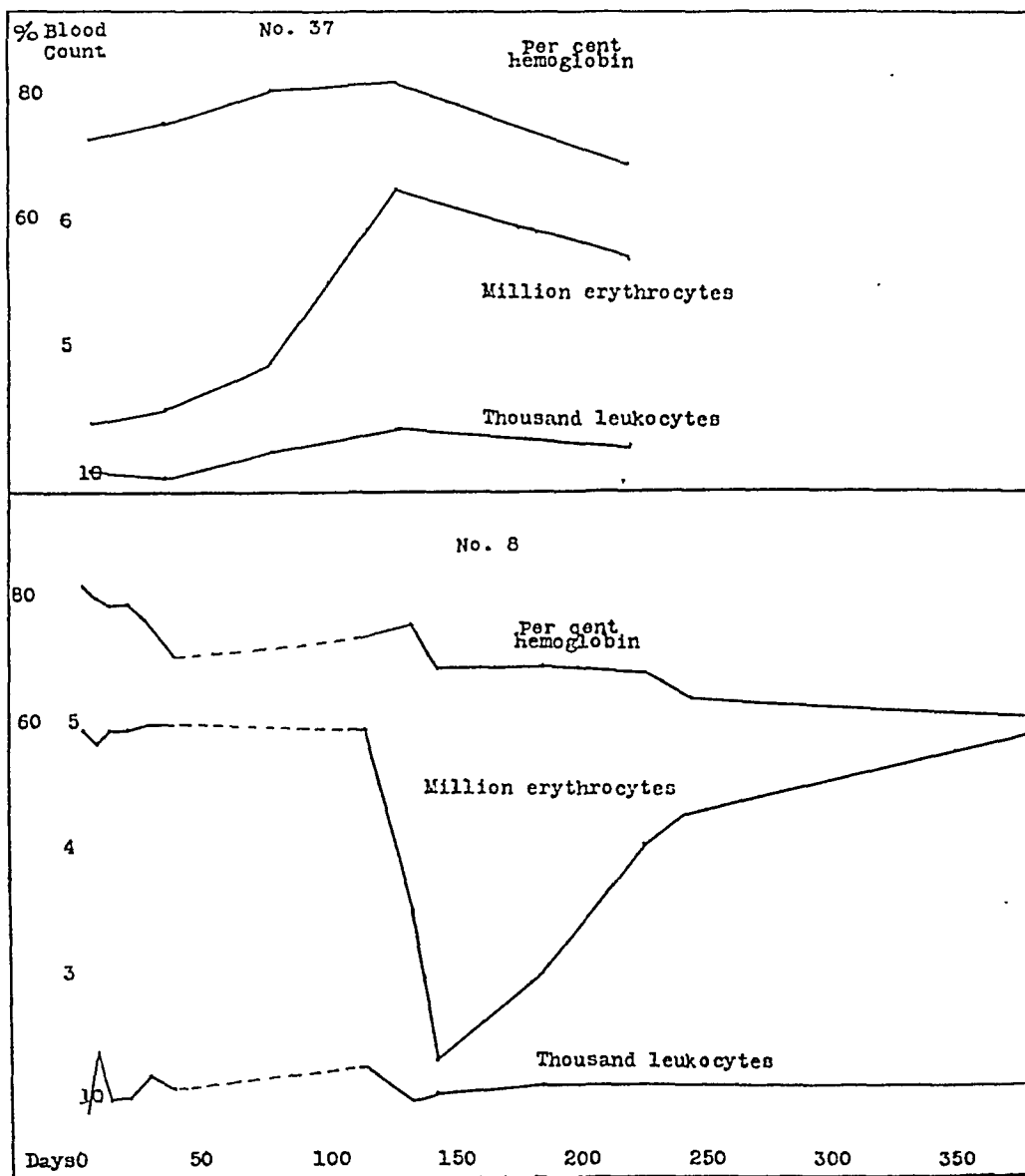


Chart 7.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits fed daily 0.1 Gm. each of sodium aluminum sulphate. The dotted line represents a period during which the feeding of the aluminum salt was suspended.

Whether this somewhat consistent decrease in percentage of hemoglobin and the occasional marked depression in the number of erythrocytes is mere chance or whether it is significant may possibly be

decided by noting whether any considerable effects follow the feeding of large doses. If acute effects can be produced by the latter means, then are we not justified in suspecting that slight similar effects repeated over years may lead to chronic symptoms with a gradual failing of the hematopoietic system and the attending lowered resistance? It seemed worth while, therefore, to study the effects following the feeding of large doses of aluminum.

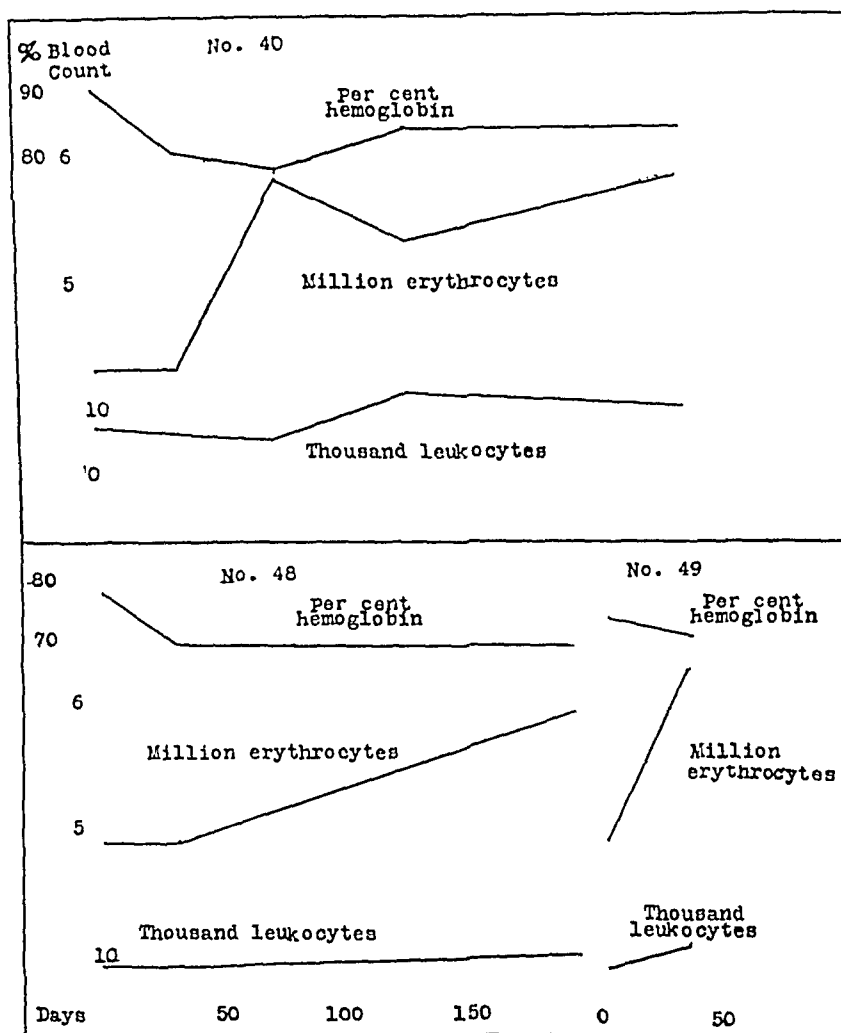


Chart 8.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits daily fed lactose only. These were controls on the rabbits fed sodium aluminum sulphate, which was mixed with lactose.

#### FEEDING OF A SINGLE LARGE DOSE OR A FEW LARGE DOSES OF ALUMINUM COMPOUNDS

*Results with  $AlCl_3 \cdot 6H_2O$ .*—Rabbit 55 (1.5 Kg.) was fed 1.5 Gm. of aluminum chloride ( $AlCl_3 \cdot 6H_2O$ ) in gelatin capsules. In fifteen minutes, it began to breathe hard, displayed the motions of vomiting, stretched at length prostrate and jerked its head from side to side. It

then seemed to improve for a while, but after two hours died in convulsions. Autopsy revealed much liquid, containing aluminum, in the stomach, much mucous secretion and black hemorrhagic areas on the mucosa. The fluid in the stomach darkened blood when it came in contact with it, as does the aluminum ion.

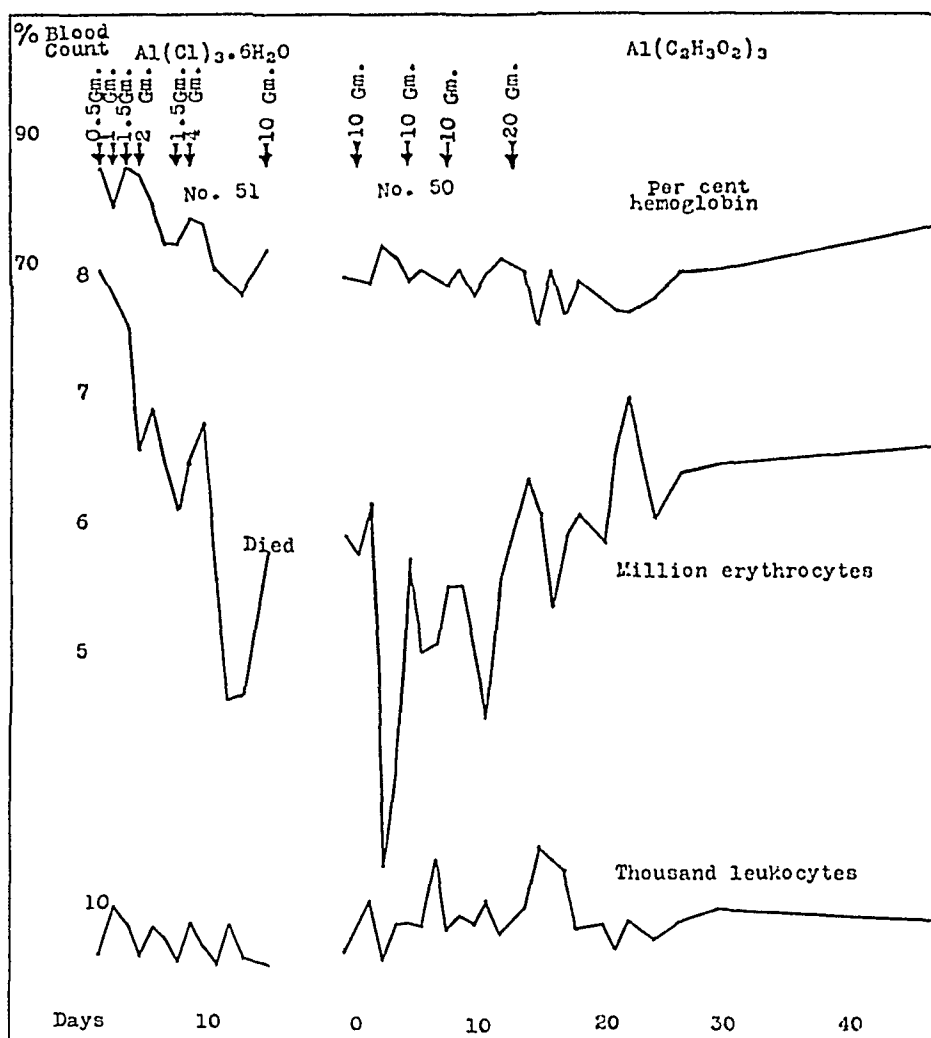


Chart 9.—The individual hemoglobin, erythrocyte and leukocyte curves of two rabbits following the feeding of single large doses of aluminum compounds over a period of fourteen days. An arrow indicates the time and the amount of each feeding.

Another rabbit, no. 51 (3 Kg.), was fed large single doses of aluminum chloride in gelatin capsules, ranging from 0.5 to 10 Gm. during a period of fourteen days. On chart 9, the arrows indicate the times of feeding and the amounts are mentioned. The total fall of over 3,000,000 in the number of erythrocytes and the fall of 18 per cent in hemoglobin, as well as the individual decreases after each dose, are striking. It is

noteworthy that the effect is registered soon after each feeding. This is indicative of a real toxicity of the aluminum, rather than of an impairment of digestive functions, which would lead to similar changes only later. There was no loss in weight. The rabbit finally died as a result of a feeding of 10 Gm.

The autopsy was performed within less than two hours after death. There were hemorrhages in the stomach, the mucosa of the whole small intestine was blanched, as if macerated, and there was a complete loss in tonus of the entire tract. The spleen was spongy, flabby and engorged; the kidney was small and soft and the cut surface was abnormal.

Microscopic examination showed marked changes in the kidney, which were essentially the effects produced by toxic agents. Changes suggesting the same condition were found in the spleen, and the lesions in the spinal cord were especially interesting.

The detailed protocols of the microscopic observations in rabbit 51 follow:

The liver was normal.

The spleen showed slight fibrosis of the pulp and slight diffuse pigmentation. In the pulp was blood pigment in phagocytes. Occasionally, large phagocytes contained both pigment and cells; also there were occasional areas of coagulated material not containing cells. There were numerous clumps of cells resembling somewhat cellular thrombi, although no distinct vessel wall could be seen about them, and there were also areas of hemorrhagic infiltration of the pulp.

The kidney showed swollen convoluted tubules, with, as a rule, no lumen remaining. There was practically no staining of nuclear material in the cells of the convoluted tubules. The epithelial lining appeared as solid coagulated masses, generally shrunken from the basement membrane. Loss of staining was so complete as to resemble an advanced postmortem autolysis, which can be excluded by the fact that the animal was sectioned two hours after death. Furthermore, the fusion of the renal epithelium into solid, structureless, granular masses, in places resembling granular casts, indicates that there had been a marked antemortem destruction of the swollen epithelium of the convoluted tubules in toto. Rarely, a cell was found in the convoluted tubular epithelium that retained nuclear stain. The nuclei of the basement membrane of these same tubules stained well, as did the nuclei of the loops of Henle, although these cells were swollen and often separated from one another. The collecting tubules showed swollen epithelium, the lumen rarely being visible, but the nuclei stained well. The glomeruli retained their nuclear staining. The tufts were generally swollen, but no hemorrhage or exudation was seen. The appearance indicated a selective toxic necrosis of the epithelium of the convoluted tubules.

The spinal cord showed marked destruction of the cytoplasm of many of the ganglion cells, some of which exhibited little besides the nucleus, containing many vacuoles and a granular detritus filling up the space formerly occupied by the ganglion cell. All the ganglion cells were more or less affected the same way. The white matter was also greatly vacuolated and granular.

The lung contained many small hemorrhages, slight edema and marked engorgement of the vessels. There was no inflammatory reaction. The red corpuscles seemed to be discrete, and hyaline thrombi were not recognized.

The stomach showed a diffuse loss of nuclear stain. There was no sharp necrosis, no inflammatory reaction. The vessels were engorged with blood.

The adrenal glands stained well and showed no recognizable alterations.

The duodenum showed a necrotic condition of the superficial portion extending about half through the mucosa, accompanied by a marked accumulation of stringy, blue-staining material, apparently mucin. There was no inflammatory reaction.

Lest the effects observed in these two experiments might be solely due to the acid liberated from the chloride compound, other aluminum compounds were similarly used.

*Results with  $Al(C_2H_3O_2)_3$ .*—Rabbit 50 (3.8 Kg.) was fed four times, at five day intervals, 10 Gm. of  $Al(C_2H_3O_2)_3$  in approximately 100 cc. distilled water by stomach tube (chart 9). Before each feeding, the rabbit had been starved over night to insure a fairly empty stomach. In this experiment, the decrease in the number of erythrocytes after each feeding is striking, but not lasting, and in the final rebound the level is higher than it was originally. The percentage of hemoglobin is not seriously lowered, although there is evidence of a slight decrease after some of the feedings. Thirty-three days after the fourth feeding, this animal was killed by a blow on the back of the head and examined immediately. The histologic observations were as follows:

The lungs showed no change.

The liver showed slight fatty degeneration in the liver cells, nowhere marked, but diffuse through all parts of the lobule. There were vague masses staining red with scarlet R, some of which were in the blood vessels and some in the sinusoids. The nature of these is not clear, but their location raises the question whether they can be agglutination thrombi. A section of the same liver stained with hematoxylin and eosin showed in some of the vessels masses of fused red corpuscles corresponding in shape and size to the masses that stained red with fat stains. When the specimen stained with scarlet R was counter-stained with hematoxylin, it was seen that some of the fat masses corresponded to large, fatty liver cells or to Kupffer's cells, but there were also masses staining like fat which plugged the sinuses.

The heart showed no change, and no fatty degeneration.

The duodenum showed diffuse loss of staining in its surface layers, occasional submucous hemorrhages. The excretory ducts of a few of the Brunner's glands were packed with leukocytes, although there were no changes in the adjacent tissues.

The adrenal glands revealed no change.

The spleen was generally normal in structure, except for occasional accumulations of brown pigment in masses, not generally in phagocytes.

The stomach was normal.

The kidney presented epithelium somewhat swollen and vacuolated. There was no fatty degeneration of the epithelium, but there were occasional irregular masses of fat stain, the location and nature of which could not be accurately determined.

Rabbit 730 (2 Kg.) was fed 30 Gm. of  $\text{Al}(\text{C}_2\text{H}_3\text{O}_2)_3$  in a single dose in 100 cc. of water by stomach tube. Although it seemed to be all right following the feeding, on the third day it was found dead. At autopsy, the adrenal gland was normal. The spleen was small, thin and somewhat congested in areas. The stomach was filled with a brownish watery suspension, the muscles lacked tonus and the mucosa was completely coagulated into granular white folds. The small intestine seemed normal, but was filled with a jelly-like, yellowish-green substance. The heart was somewhat distended with venous blood, and showed profound fatty degeneration. In the lungs were many patches that looked extremely hemorrhagic and these were interspersed with pale areas. On cutting, much dark blood oozed out. The microscopic observations were as follows:

In the lung, areas of edema were present without inflammatory change, and the vessels were engorged with blood. The testicle showed no spermatogenesis. There was no atrophy, but the spermatids and spermatozoa were entirely lacking. Many large multinucleated cells were present in the tubules. The epididymis contained no spermatozoa. The kidney showed profound fatty degeneration in all the straight tubules; the epithelium was much swollen, granular and finely vacuolated, occluding the lumen. Fat droplets were present in the convoluted tubules and glomeruli and also in the intima of the blood vessels. In the liver were branching streaks that took the fat stain, and the size and location of these streaks corresponded to those of the capillaries, but there was no fat in the liver cells. The fat masses were generally too large to correspond to the Kupffer cells. In the centers of some of the lobules, however, there was slight fatty degeneration in the liver cells. In some places, where the capillaries contained blood, the material that stained like fat could be seen definitely to be in the walls of the blood spaces. The sinuses of the spleen were much dilated and contained many granular masses and some resembling agglutinated red corpuscles as well as disintegrated red corpuscles. There were masses of mucus present on the surface of the stomach and extending slightly into the lumen of many of the glands. The glands near the surface were disorganized, but no inflammatory changes were seen.

*Results with Metallic Aluminum.*—Rabbit 53 (2.5 Kg.) was fed only two doses (3 and 4.5 Gm.) of powdered metallic aluminum in gelatin capsules (chart 10). The fall of 2,000,000 in erythrocytes and of 22 per cent in hemoglobin is good evidence that the aluminum goes into solution in the digestive juices and is absorbed. These decreases are further evidence that the changes in the blood noted in some of the previous experiments were due to the aluminum ion itself rather than to any acid radical accompanying it. Thirty-nine days after the last feeding, this rabbit was killed by a blow on the head and examined immediately. Few pathologic changes were noted. In the kidney, the renal epithelium was slightly swollen and granular, but the lumen usually persisted and in some of the tubules the epithelium was much vacuolated. There were no casts. Marked fatty changes were seen in the Kupffer cells, but no fat was seen in the liver cells.



Rabbit 771 (2 Kg.) was fed metallic aluminum in the following doses on four consecutive days: 2, 1.7, 2 and 2.1 Gm., respectively. Twenty days after the last feeding the rabbit was found dead, and the autopsy indicated that death was probably due to an infection of the lungs. The spleen was small and dark; the stomach and duodenal mucosa were blanched and the stomach was filled with gas.

Microscopically, the spleen was enormously engorged with blood, and the sinuses were greatly distended with blood, but without thrombosis or necrosis. The lungs showed acute suppurative pleuritis, which may account for the focal

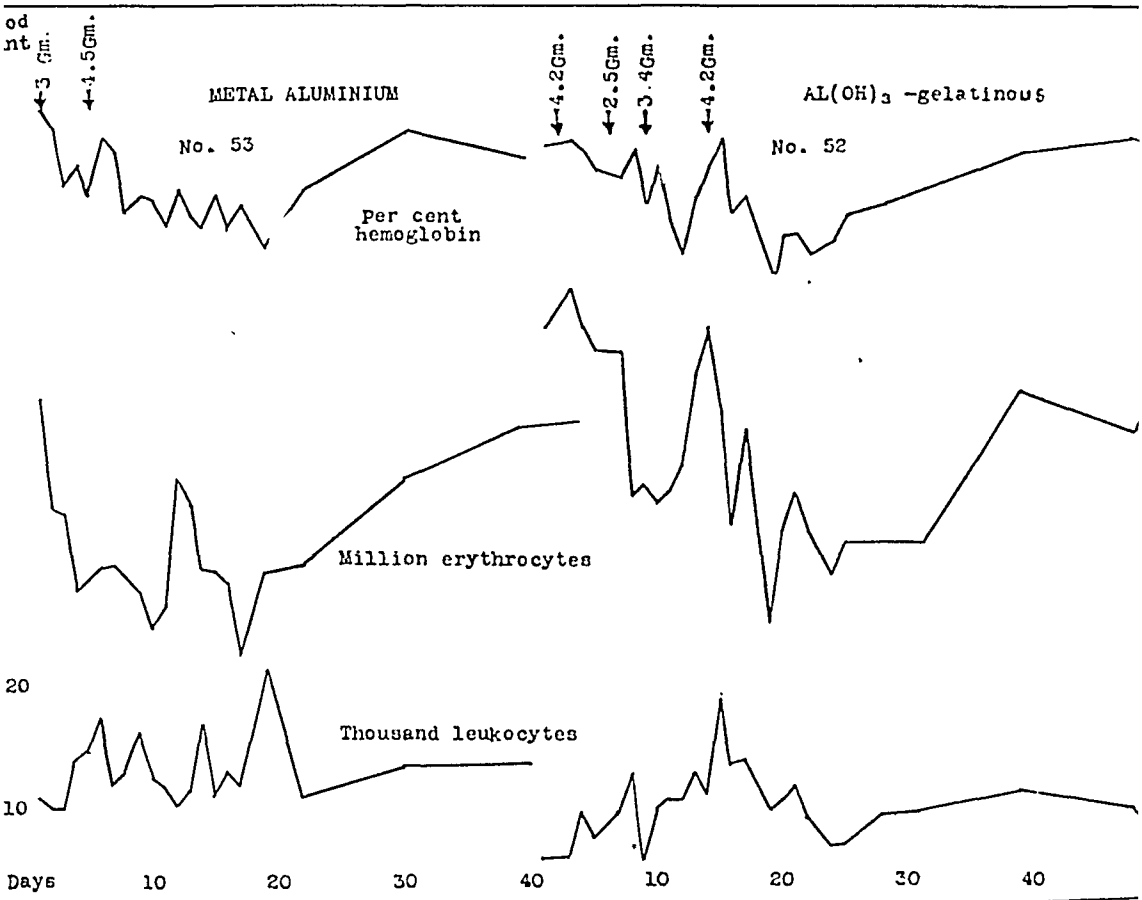


Chart 10.—The individual hemoglobin, erythrocyte and leukocyte curves of two rabbits fed aluminum compounds as follows: rabbit 53, metallic aluminum, and rabbit 52, Al(OH)<sub>3</sub> (gelatinous). An arrow indicates the time and the amount of each feeding.

necrosis in the liver. The tubular and cortical epithelium of the kidney was swollen and the glomeruli were much engorged with blood. In the liver, the centers of the lobules showed a decreased number of cells and loss of cord arrangement, and the liver cells here seemed somewhat coagulated, although they preserved their nuclei, which tended to be pyknotic. There were small areas of early focal necrosis and fatty changes in some of the Kupffer cells without fat in the liver cells.

*Results with  $Al(OH)_3$ .*—Since the aluminum ion, as it is usually ingested with foods, is chiefly in the form of  $Al(OH)_3$ , rabbit 52 (2.75Kg.) was fed with  $Al(OH)_3$ ,<sup>15</sup> suspended in from 50 to 100 cc. of distilled water.

This suspension was fed by stomach tube to the fasting rabbit, over a period of from two to five hours, according to its ability to tolerate the aluminum. The accompanying curves of rabbit 52 (chart 10) show that this compound was apparently absorbed just as were the other aluminum compounds. The drop of 2,600,000 in erythrocytes and of 20 per cent in hemoglobin is evidence that the compound does not all pass on through the alimentary tract as inert material. When this rabbit was killed forty days after the last feeding no pathologic changes were found, gross or microscopic.

Rabbit 750 (2.5 Kg.) was fed, at one time, by stomach tube, 40 Gm. of  $Al(OH)_3$  suspension prepared in the same manner as that described for the preceding experiment. At the end of three days, it was moribund. It was killed with ether and examined immediately. The stomach contained nothing except a watery mucous substance filled with dark brown blood clots, some of which were also on the mucosa. The same condition was observed in the duodenum. The lungs also contained hemorrhagic spots, and red and white patches. The blood was almost black, and ran freely. Otherwise, the tissues were normal.

The microscopic changes noted were chiefly those of fatty degeneration. In the kidney, the convoluted tubules and Henle's loops were chiefly involved, and the collecting tubules and the pyramids showed but slight fatty changes. The blood capillaries were often filled with agglutinated and hemolyzed red corpuscles, forming thrombi. The glomeruli showed only occasional dustlike fat droplets. Homogeneous pink-staining material was found in the vessels of the heart and of the liver and marked fatty degeneration of the parenchyma cells was present. In the liver, the degeneration was least marked about the portal triads. In the lung, a few of the bronchioles contained leukocytes, but there were no pneumonic changes. A few leukocytes were found in the alveoli and alveolar walls. The blood in the small vessels had a brassy appearance, and in some it was hemolyzed. The testicle seemed normal. In the stomach was an area of superficial ulceration, in which were many polymorphonuclear leukocytes. These extended into many of the gastric glands, even those at considerable distance from the site of the ulcer. There were many mitotic figures in the glandular epithelium in this vicinity. The spleen was poor in lymphoid tissue and the pulp diffusely fibrotic. There was much brown pigment. There were many small masses of iron and extensive deposits in the capsule and trabecula, but only a faint iron stain in many of the phagocytes. The larger masses of dark brown material did not stain for iron.

15. The  $Al(OH)_3$  was prepared as follows: 50 Gm.  $Al_2(SO_4)_3 \cdot Na_2SO_4 \cdot 24H_2O$  was dissolved in distilled water. Enough strong sodium hydroxide was added to neutralize the solution and to precipitate the aluminum as  $Al(OH)_3$  in the form of a gelatinous mass. This precipitate was then filtered off and washed with hot water to free it from other soluble salts. The washed precipitate was then ground to a creamy paste in a mortar with about 100 cc. of distilled water.

Again 45 Gm. of a suspension of  $\text{Al}(\text{OH})_3$ , made as previously described, was fed to rabbit 775 (2.3 Kg.) by stomach tube. The rabbit died suddenly four days later, probably from peritonitis caused by a perforation in the stomach, which was full of a black mash intermingled with some loose, white, mucous masses. There was considerable hemorrhage around this perforation. The lungs were full of raised white patches and dark red areas.

Microscopically, no changes were found in the liver, testicle, lungs and spleen (except postmortem changes). A few glands in the duodenum were dilated. The kidney showed marked postmortem changes. The peripheral portion was well fixed, but showed no definite changes, and there were also no fatty changes, as determined by special staining, except that the protoplasm of the epithelium of the convoluted tubules stained diffusely a little more than other elements.

$\text{Al}(\text{OH})_3$  may exist in two forms—either as a gelatinous compound, which readily dissolves in the slight acidity or alkalinity of the digestive juices, or in a more granular form, which is supposed to be extremely insoluble. Two more experiments were therefore planned. For these, the solution containing 50 Gm. of sodium aluminum sulphate ( $\text{Al}_2[\text{SO}_4]_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ ) was neutralized, changing it to  $\text{Al}(\text{OH})_3$ , and washed, and the final suspension of gelatinous  $\text{Al}(\text{OH})_3$  was boiled two hours over a direct flame to change it to the granular, insoluble form. This process is comparable to what might happen to a greater or less extent in baking.

Rabbits 54 to 56 were fed by stomach tube with three doses each of this compound and chart 11 shows that even this presumably insoluble compound must have been absorbed, for the effects on the erythrocytes and the hemoglobin were similar to those obtained in the former experiments.

Rabbit 56 (2.7 Kg.) was fed its third dose of  $\text{Al}(\text{OH})_3$  at 4 p. m., and at 10 p. m. it seemed to be perfectly normal, with the exception of a slight diarrhea. (Rather severe diarrhea frequently followed some of the feedings.) The next morning, the rabbit was found dead. At autopsy, the stomach was found to be full of a brown mush mixed with a white, slimy precipitate, and the wall was thin and hyperemic. The small intestines were filled with a watery brown mixture, and the colon was distended with a thin, watery brown liquid.

Microscopically, the changes in the kidney resembled those found in another rabbit (51), which died as a direct effect of feeding aluminum chloride ( $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ ). In the lungs, agglutination thrombosis was found, so extensive as to have been the probable cause of death. This is significant in connection with death from ingested aluminum, for it has been shown that aluminum is a strong agglutinating reagent with red corpuscles. The protocols of the histologic examinations follow:

The epithelium of the kidneys was swollen so that the lumen was often occluded. Occasionally, granular casts and loose cells were seen. Many of the cells of the convoluted tubules contained yellowish-brown material in granules, sometimes occupying vacuoles. It was not as dark brown as hemosiderin and had more the appearance of hemoglobin. A large proportion of the convoluted tubules showed this change. There were occasional hyaline casts and occasional tubules in which the epithelial cells were disintegrated and lay in loose masses filling up the tubules. There was no frank coagulation necrosis. The glomeruli generally seemed to be normal. The collecting tubules had swollen epithelium, but otherwise seemed normal.

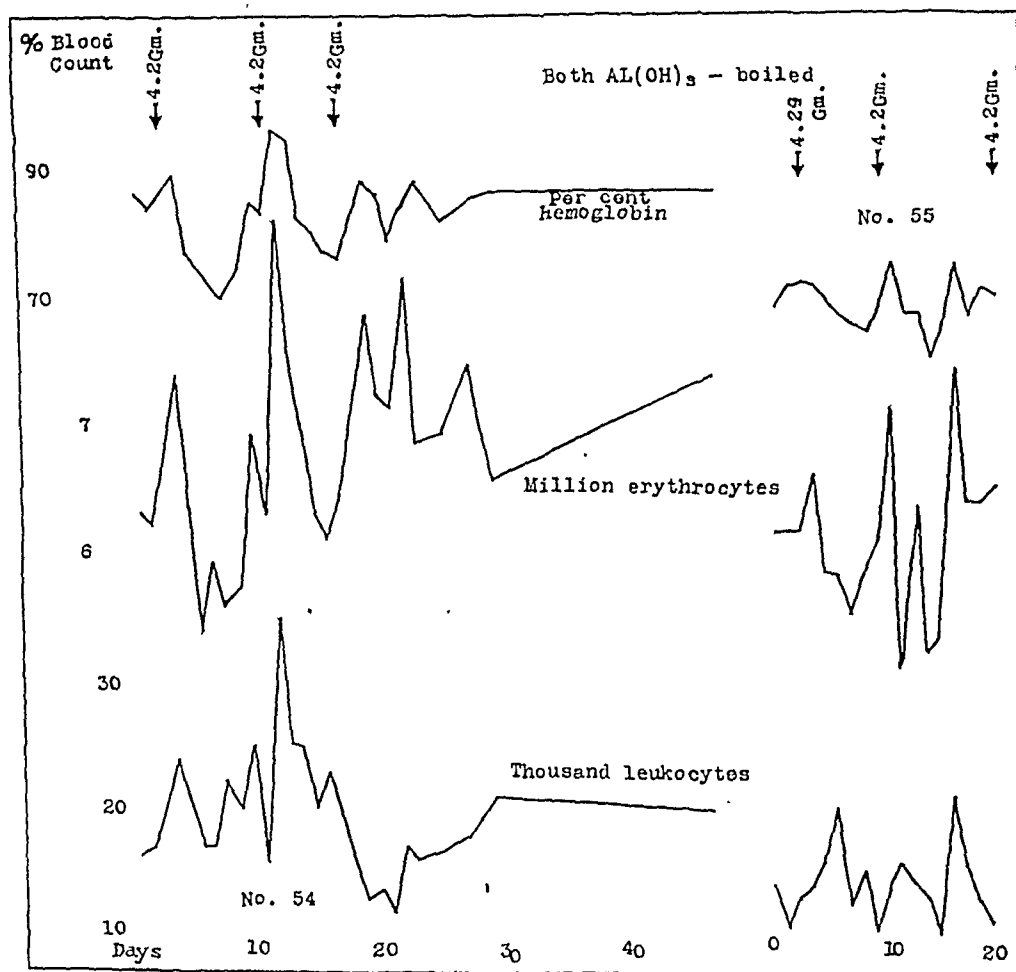


Chart 11.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits fed three large single doses each of a boiled aluminum compound  $Al(OH)_3$  in the amounts and at the intervals indicated by the arrows.

The adrenal glands were normal.

The lungs showed marked engorgement of vessels with occasional small hemorrhages into the alveoli and edema involving perhaps one fourth of the alveoli. Some of this edematous fluid was also present in the bronchi. The capillaries were distended with masses of homogeneous structure, apparently thrombi from agglutination of red corpuscles. In the larger vessels, the red corpuscles were usually discrete. This condition of capillary agglutination thrombosis was extremely marked. There was no inflammatory process.

The myocardium was normal.

The stomach showed diffuse loss of stain on the surface, apparently post-mortem.

The pancreas and the duodenum revealed no changes.

The spleen showed no pigmentation, hemorrhage or necrosis, except for an occasional phagocytic cell containing brown granules. The fibrous elements of the pulp were more conspicuous than usual.

The testicle showed spermatogenesis present but not abundant.

When the other rabbit, no. 54 (2 Kg.), which was fed boiled Al (OH)<sub>3</sub> also was killed, the tubular epithelium of the kidneys was generally normal, but in a few of the glomeruli, the capillaries were distended and contained homogeneous red cells, apparently thrombi from agglutination, but no hemorrhage or exudation. There was slight fatty degeneration in a few of the convoluted tubules and the endothelial cells. A few of the capillaries were plugged with masses staining for fat. The capillaries of the lungs were distended with homogeneous masses of red cells—agglutination thrombi—but there was no edema or hemorrhage. In sections of the liver stained for fat and counterstained with hematoxylin, there were many red masses corresponding in size and shape with single large liver cells, each with an intact nucleus surrounded by a solid mass of fat droplets, although the great majority of the liver cells contained no fat despite the fact that all the cells were deeply vacuolated. There were also smaller masses of stain that seemed to correspond to Kupffer's cells. Another section showed masses of fat granules, some corresponding to enlarged liver cells, others to Kupffer's cells, the latter being especially conspicuous in this liver. There were also masses of agglutination thrombi filling sinuses and small blood vessels.

The effects on the leukocytes in these rabbits fed large doses of aluminum compounds were plotted (chart 11) also, and occasionally a marked disturbance was noted.

A study of the blood pictures in these animals showed marked polychromasia, slight poikilocytosis and anisocytosis and an occasional normoblast and stippled cell.

#### EFFECT OF ALUM ON THE PRODUCTION OF COMPLEMENT AND ANTIBODIES

The experiments to determine the effects of aluminum on the production of complement and antibodies fall into four groups. Group 1 consisted of the control tests, in which one rabbit, no. 7 (2.7 Kg.), received a single injection of 5 cc. of a 50 per cent solution of washed sheep cells, and two rabbits, nos. 23 (2.9 Kg.) and 24 (2.8 Kg.), each received two injections of sheep cells seven days apart. Hemolysins and agglutinins were followed in each rabbit (chart 12). The development of agglutinin was followed by not adding complement to every other tube in the titration. A small amount of hemolysin was found following a single injection of sheep cells; but practically no agglutinin was demonstrable. There was a sudden rise, however, in both antibodies following a second injection of sheep cells. The chart shows, furthermore, an increase in native complement (fine dotted line in chart), following the second injection of sheep cells. The experiments are reported because

the contrast is so great between the results in groups 1 and 2 and those in groups 3 and 4 (with rabbits receiving considerable quantities of aluminum compounds) as to indicate strongly that decided effects result from injections of aluminum.

Group 2 consisted of three experiments in which rabbits 6, 21 and 25 (2.9 Kg. each) were each given an injection of sheep cells, followed

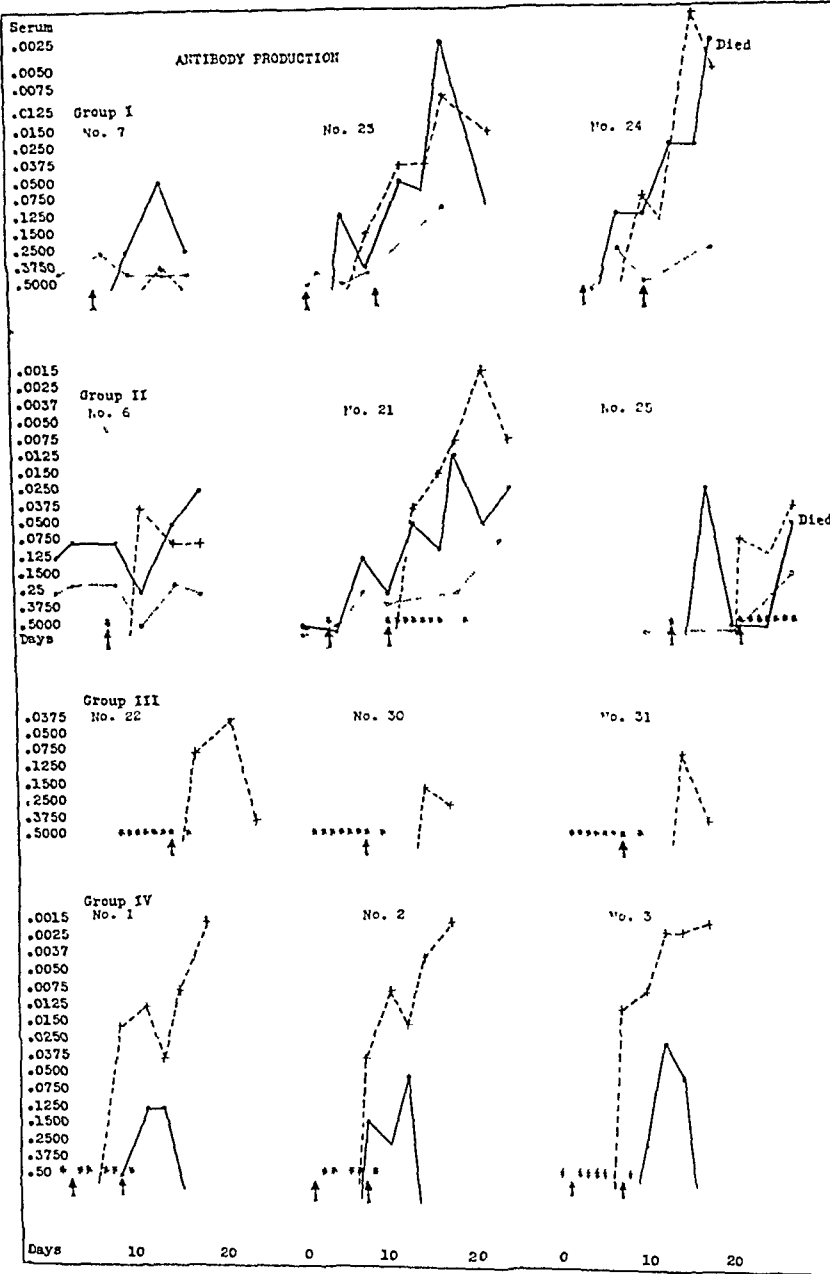


Chart 12.—The individual hemolysin, agglutinin and complement curves of rabbits treated with aluminum. The solid line represents hemolysin, the dash line agglutinin and the dotted line complement. An arrow indicates the day of injection of 5 cc. of a 50 per cent dilution of sheep cells. A star indicates the day of injection of  $\text{Al}_2(\text{SO}_4)_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ . A double-hilted dagger indicates the day of injection of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ .

by an injection of 0.04 Gm. of  $\text{Al}_2(\text{SO}_4)_3 \cdot 24\text{H}_2\text{O}$  in 5 cc. one hour afterward. Here, also, some hemolysin was produced, but little, and practically no agglutinin. Rabbits 21 and 25 were then each given a second injection of sheep cells seven days after the first injection, and then injections of alum for seven consecutive days. Rabbit 25 died immediately following the seventh injection of alum. In rabbit 21, the hemolysin rose following the second injection but never as high as in the controls; the agglutinin, however, rose high. In rabbit 25, little of either agglutinin or hemolysin was demonstrable. The remarks made concerning complement in group 1 are true also for this group.

Group 3 consisted of three experiments, in which the rabbits, no. 22 (2.7 Kg.), no. 30 (2.4 Kg.) and no. 31 (2.4 Kg.), were given injections of alum on seven consecutive days prior to the injection of the sheep cells. In all three cases, no hemolysin was demonstrable, and only a small amount of agglutinin. These results are therefore to be contrasted with the results in the control animals, in which after a single injection of sheep cells there was a small production of hemolysin, but practically no demonstrable agglutinin.

Group 4 consisted of three experiments in which rabbits 1, 2 and 3, which were showing a definite picture of anemia following extended injections of aluminum solutions (charts 1 and 4), were tested for production of antibodies. Rabbit 1, which had received forty-four previous injections of alum, was given an injection of sheep cells, then four more injections of alum, and a second injection of sheep cells six days after the first, as indicated on the chart. Rabbit 2, which had received thirty-two previous injections of alum, was treated similarly. Rabbit 3, which had received forty previous injections of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ , was also treated like nos. 1 and 2. All three showed marked production of agglutinin after the first injection of sheep cells, but no demonstrable hemolysin. Following the second injection of sheep cells, in all three rabbits, hemolysin appeared for only a short period, but the agglutinins were markedly increased. During the determinations of agglutinin, it was noted that there was a peculiar heavy precipitate in the tubes. This opens the question whether, in view of the lack of formation of hemolysin, the apparent increase in agglutinin might not really be added evidence concerning the poisoned condition of the blood, rather than a true formation of antibodies. It had been previously shown that during the poisoning of the blood with aluminum compounds the corpuscles became more resistant to hemolysis by saponin and hypotonic salt. Therefore, it seems possible that an increase in aluminum in the serum, due to injection of the aluminum compounds, prevents hemolysis of the sheep cells used in the test and at the same time causes marked agglutination of these same cells, thus giving the appearance of an increased formation of agglutinin.

## COMMENT

From the results obtained in the experiments in which aluminum compounds were injected directly into the blood stream of rabbits, we conclude that the aluminum ion, introduced either combined as the sodium sulphate salt or as the chloride, produces a marked anemia, and when the dose is large enough, even causes death.

When daily intravenous injections of these two compounds were given, a definite secondary anemia was produced, i.e., there was a decrease in the percentage of the hemoglobin and in the number of the erythrocytes, an increase in the number of the leukocytes, chiefly the mononuclears, and an increased resistance of the corpuscles to hemolysis by hypotonic salt and saponin. Such increased resistance of the blood cells to hemolytic agents has been linked in lead poisoning with an increase in fragility of the corpuscles and denotes an injury to the cells. The final blood picture is also morphologically similar to that found in the later stages of lead poisoning, there being present normoblasts, poikilocytes, anisocytes, chromatophilic cells in considerable numbers and a few stippled cells.

Moreover, local irritant effects appear at the site of the injection—swelling, edema, inflammation and necrosis of the tissue and swelling of the neighboring lymph glands. All these symptoms were somewhat more marked in rabbits receiving injections of sodium aluminum sulphate than in those receiving injections of aluminum chloride.

These results are not wholly due to acid, since no similar effects were produced when a sulphuric acid solution of the same  $p_H$  as the solution of sodium aluminum sulphate was injected. A decrease in the number of erythrocytes, however, occurred when a sulphuric acid solution of  $p_H$  2.6 was injected daily. This acidity corresponds to the maximal acidity that could be released from the alum compound, but it is improbable that a release of so much acid from alum would ever occur suddenly enough and at one time in the blood stream to give rise to the same effect as is produced by the injection of a solution of  $p_H$  2.6.

A study of the minimal lethal dose emphasizes the toxicity of aluminum compounds. Rabbits seemed to be able to tolerate daily intravenous doses of from 0.011 to 0.017 Gm. of sodium aluminum sulphate in 0.8 per cent concentration, per kilogram, and from 0.003 to 0.004 Gm. of aluminum chloride, per kilogram, for as long as forty days, or a total of 1.5 Gm., or of from 0.416 to 0.625 Gm. per kilogram, of the former salt, before they showed visible signs of decline to such an extent that it seemed inadvisable to continue the injections without an interval of rest. However, as small a single dose as 0.25 Gm., when given in a solution of 2.5 per cent concentration, killed a rabbit weighing 1.8 Kg. immediately. This same amount (0.25 Gm.) was nonlethal when given at one time in a large volume of solution or in the concentra-



tion of 0.8 per cent to another rabbit of the same size. When 0.73 Gm. was given to this rabbit over a period of four days, death did not occur immediately, but the rabbit rapidly weakened and died twenty-four days later. A third rabbit of the same size died after receiving 0.76 Gm. over a period of seventeen days. Therefore, although a total as high as 1.5 Gm. or from 0.416 to 0.625 Gm. per kilogram of sodium aluminum sulphate could be tolerated, if given over a period of forty days, one-half that amount was lethal if given in a shorter time in the same concentration, and one sixth as much was lethal if given at one time in greater concentration.

A study of the tissues of all these rabbits revealed many lesions; namely, focal necrosis, infiltration with round cells and vacuolization of the liver cells; pigmentation, fibrosis, thrombosis and necrosis of the spleen; vacuolization of the renal epithelium and granular degeneration, necrosis and spontaneous nephritis in the kidney; lytic changes in the heart muscle cells; petechiae and ulcers in the stomach and intestines, etc. Except for the intestinal and splenic lesions, none of these lesions was found consistently in the alum-treated rabbits alone, and therefore they cannot be considered exclusively the result of treatment with aluminum compounds. It is significant that both rabbits killed by the intravenous injection of 0.73 and 0.76 Gm. of sodium aluminum sulphate over periods of from four to seventeen days showed extensive necrosis in the splenic pulp, while this never was seen in any of the control rabbits or in those that were fed alum. Similar lesions of varying degree were found in the spleens of several other animals that received aluminum, but not in the controls. Apparently, they resulted from injury to the blood, with formation of agglutination thrombi in the spleen sinuses.

These experiments leave no doubt that aluminum compounds are toxic and even lethal when put directly in contact with the blood and the tissues. There was still the question whether similar results can occur from feeding or whether the aluminum as usually ingested, i.e., in the residues of baking powder, may not be in such an insoluble form that it cannot be absorbed and therefore cannot produce these toxic symptoms.

Two sets of feeding experiments were undertaken in order to determine this point. In the first series, small daily doses of sodium aluminum sulphate (0.1 Gm. as  $\text{Al}_2[\text{SO}_4]_3 \cdot \text{Na}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ , which is the equivalent of from 0.0007 to 0.0011 Gm. aluminum per kilogram per day) were fed to rabbits weighing from 2.5 to 4 Kg. In these experiments, extending over varying periods of time up to one year, no outward clinical symptoms were detectable, but there was an undoubted moderate decrease in the percentage of hemoglobin in most of the rabbits. No such decrease occurred in the control rabbits. Moreover,

in contrast with the unexplainable increase in the number of erythrocytes in the control rabbits fed only lactose, there were marked decreases, at times, in the number of erythrocytes of the rabbits fed the aluminum compound.

That dramatic effects, such as follow intravenous administration, cannot be expected to result from feeding the same compound is illustrated by the experiments of Sollman<sup>15</sup> with  $\text{Pb}(\text{CO}_3)_2$ . Daily feeding of  $\text{Pb}(\text{CO}_3)_2$  (0.15 Gm. per kilogram or 0.11 Gm. Pb per kilogram) to rats produced no effect in thirty-five weeks, except loss of appetite and checking of growth. And yet no one doubts the harmfulness of lead as an article of food.

Aluminum is particularly toxic to red corpuscles, and it may well be that, in analogy with chronic lead poisoning, years of slow absorption of minute amounts of aluminum are required to effect the same results that are accomplished in a short time by introducing the substance directly into the blood stream. That this is a possibility is suggested by the slight changes noted in the blood after prolonged feeding of small doses of an aluminum compound.

The strongest evidence, however, that the feeding of aluminum compounds, in any form, including that supposed to be so insoluble and inert ( $\text{Al}[\text{OH}]_3$ ) may be harmful, lies in the results obtained in the second series of feeding experiments with large single doses of aluminum compounds. Quick responses, such as decreases of from 2,000,000 to 3,000,000 in the number of erythrocytes and of as much as 20 per cent in the hemoglobin were noted in a day or two following the ingestion of large doses of aluminum, in the form of  $\text{Al}(\text{Cl}_3 \cdot 6\text{H}_2\text{O})$ ,  $\text{Al}(\text{C}_2\text{H}_3\text{O}_2)_3$ , metallic aluminum,  $\text{Al}(\text{OH})_3$  (soluble gelatinous form) and  $\text{Al}(\text{OH})_3$  (granular insoluble form).

Death followed immediately after the ingestion of  $\text{Al}(\text{Cl}_3 \cdot 6\text{H}_2\text{O})$  in two rabbits (1.5 Gm. equaling 0.16 Gm. metallic aluminum, in a rabbit weighing 1.5 Kg. and 10 Gm., equaling 1.3 Gm. metallic aluminum, in a rabbit weighing 3 Kg.). One rabbit died during the night following a feeding of insoluble  $\text{Al}(\text{OH})_3$  (4.25 Gm., equaling 1.47 Gm. metallic aluminum in a rabbit weighing 2.7 Kg.). The other rabbits either died three, four or more days after the feedings or were killed at the end of a month.

At autopsy, these rabbits showed chiefly toxic effects in the kidneys, such as marked swelling of the tubular epithelial cells, in one with fusion of the cells into solid, structureless, granular masses resembling casts, with loss of nuclear staining. Thrombi from agglutination were especially prevalent in the lungs, liver and kidneys in some of the rabbits, and attention is called to the apparent relationship between this

15. Sollman, T.: J. Pharmacol. & Exper. Therap. **19**:375, 1922.

phenomenon and the hemagglutinative effect of aluminum. Fatty degeneration was found in the liver, kidneys and heart in most of them. Such changes were not seen in any of the control rabbits or in those fed smaller doses of aluminum.

That these lesions, as well as the marked and sudden although transient anemias, are due primarily to the toxicity of the absorbed aluminum ion, rather than to any acid radical attached, is evident from the fact that effects follow the ingestion of the neutral  $\text{Al}(\text{OH})_3$  compounds and the metallic aluminum itself similar to those that follow the intake of acid compounds in the form of the chloride and the sulphate. There would seem, therefore, to be no doubt concerning the possibility of the absorption of aluminum following the ingestion of aluminum compounds, even when in the form of the supposedly insoluble  $\text{Al}(\text{OH})_3$ , since blood changes occur similar to those following the direct introduction of aluminum into the blood stream.

A brief preliminary study of the effect of aluminum on the immunologic defenses of the body indicated that in rabbits which were showing definite symptoms of anemia and intoxication, due to extensive intravenous injections of either sodium aluminum sulphate or aluminum chloride, two injections of sheep cells failed to increase the hemolysin, whereas the agglutinative power of the serum seemed to be greatly increased, in contrast with that of the controls. As mentioned previously, these effects may be added evidence of poisoning of the blood, rather than of a change in the production of antibodies. The experiments on this phase of the problem are scanty and are reported only because of the appearance of a distinct effect due to intoxication with aluminum and as a suggestion for further work.

#### SUMMARY

Daily intravenous injections into rabbits of from 0.011 to 0.017 Gm. sodium aluminum sulphate per kilogram in 0.8 per cent concentration, or of from 0.003 to 0.004 Gm. aluminum chloride per kilogram in 0.2 per cent concentration, caused a very definite secondary anemia, i.e., a decrease in the percentage of hemoglobin and in the number of erythrocytes, an increase in the number of leukocytes, chiefly the mononuclears, and an increased resistance of the corpuscles to hemolysis by hypotonic salt or saponin. The final blood picture showed normoblasts, poikilocytes, anisocytes, chromatophilic cells and stipple cells. Moreover, at the site of the injection, local irritant effects appeared, such as swelling, edema, inflammation and necrosis of the tissue and swelling of neighboring lymph nodes.

Daily intravenous injections of a sulphuric acid solution, the  $p_{\text{H}}$  of which was the same as that of the aluminum solution (3.4) produced no similar effects. An acid solution of an acidity equivalent to the

maximal acidity that could be, but probably would not be, released from the sodium aluminum sulphate solution at any one time ( $p_{\text{H}}$  2.6) produced a decrease in the number of erythrocytes, and in one rabbit caused marked local irritation at the site of the injection. But a comparison of the results obtained with the aluminum solutions and the corresponding acid solutions makes it probable that the changes so marked in the rabbits treated with the former were due chiefly to the aluminum ion.

The lethal intravenous dose of sodium aluminum sulphate seemed to vary inversely with the period of time over which it was given and also with the concentration in which it was given. Rabbits were able to survive from 0.416 to 0.625 Gm. per kilogram in a 0.8 per cent concentration if given over a period of forty days, whereas one half of this amount was lethal, if given in a shorter period of time in the same concentration. One sixth of the amount killed instantly if given in a 2.5 per cent concentration.

The feeding of small daily doses over extended periods of time and the feeding of large doses of aluminum compounds produced changes in the blood and the tissues which indicate that aluminum is absorbed through the intestinal tract and then exerts the same toxic effects as follow intravenous injection.

Rabbits daily fed sodium aluminum sulphate, mixed with lactose, in amounts of from 0.0007 to 0.0011 Gm. per kilogram for periods varying from 60 to 350 days, showed a greater decrease in the percentage of hemoglobin, than did the control rabbits. The number of erythrocytes occasionally decreased considerably. In a few rabbits there was a slight increase, but less than in control rabbits fed only lactose for the same length of time.

Rabbits fed at varying intervals with large single doses of  $\text{AlCl}_3$ ,  $\text{Al}(\text{C}_2\text{H}_3\text{O}_2)_3$ , metallic aluminum,  $\text{Al}(\text{OH})_3$  in soluble form and  $\text{Al}(\text{OH})_3$  in insoluble form all showed marked sudden drops in the number of erythrocytes (of 2,000,000 or 3,000,000) and in the percentage of hemoglobin (of as much as 20 per cent). The rebound, also, in most cases, was quick. Polychromasia and slight anisocytosis and poikilocytosis were found in some.

Two rabbits were killed by a feeding of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  (1 and 3.3 Gm. per kilogram) and one rabbit by a feeding of the insoluble form of  $\text{Al}(\text{OH})_3$  (1.58 Gm. per kilogram), and the pathologic changes in the kidneys, spleen (in one case), lungs and spinal cord (one case) were marked. The lesions in the kidneys resembled those of a selective toxic necrosis and the agglutination thrombi in the lungs, liver and kidneys indicate the absorption into the blood stream of the hemagglutinative agent—aluminum. Profound fatty degeneration was found in the kidneys, liver, and heart in two rabbits fed large amounts of  $\text{Al}(\text{C}_2\text{H}_3\text{O}_2)_3$  (30 Gm.) and  $\text{Al}(\text{OH})_3$  (4.05 Gm.), respectively.

In some of the rabbits treated intravenously and fed small doses of alum over extended periods, numerous pathologic lesions were found, but only the occasional lesions of the stomach or the marked changes in the spleen, namely, thrombosis, necrosis, pigmentation and fibrosis, can be considered as primarily due to the treatment with aluminum solutions, since the other lesions were often found in control rabbits, especially those with intercurrent infections. The changes in the spleen were marked and of a character indicating the presence of a poison causing damage to the red corpuscles with agglutination and hemolysis.

A few experiments on the effect of aluminum on immunologic defenses indicated that repeated intravenous injection of aluminum, to a degree leading to definite anemia, apparently reduced the capacity of the rabbits to produce hemolysin. However, the blood of these animals showed a heightened agglutinative effect, and this contradictory result raises the question whether both the heightened agglutination and the apparent lack of hemolysin may not have depended on the effect of the alum in the serum on the tested corpuscles.

# LEUKOCYTE CONTENT OF REGIONAL LYMPHATICS IN INFLAMMATION\*

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AND

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Comparatively few studies have been made of the cells circulating in the lymph. In these investigations the thoracic duct or the large lymphatic vessels of the neck have usually been used as the source of lymph. This represents the ultimate collection of lymph from various parts of the body. Davis and Carlson<sup>1</sup> found that thoracic lymph in the dog contains from 1,000 to 30,000 cells per cubic millimeter. Kindwall<sup>2</sup> obtained lymph from a point situated near the junction of the external jugular and subclavian veins, which is also the point of confluence of the thoracic duct and the lymph vessels of the neck. He reported that the cells of the lymph of the rabbit are practically all lymphocytes; monocytes were rarely found. He therefore concluded that monocytes are not produced by lymphopoietic tissues, but when found are only chance invaders of the lymph stream. Forkner,<sup>3</sup> on the other hand, recently reported that monocytes are normal constituents of all the lymph nodes of the rabbit, except the mesenteric mass. He agreed, however, that monocytes are not normally present in efferent lymphatic vessels.

A few years ago Opie<sup>4</sup> pointed out that "the local changes which with inflammation occur in the lymphatic vessels of the affected part and in the tributary lymphatic nodes are not separable from the changes which have their seat in the blood vessels and in the interstitial tissue." Within forty-five minutes after the injection of *Staphylococcus aureus*

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\* Submitted for publication, May 1, 1929.

\* From the Henry Phipps Institute, University of Pennsylvania.

1. Davis, B. F., and Carlson, A. J.: Contribution to the Physiology of Lymph: IX. Notes on the Leukocytes in the Neck Lymph, Thoracic Lymph and Blood of Normal Dogs, *Am. J. Physiol.* **25**:172, 1909-1910.

2. Kindwall, J. A.: A Supra-Vital Study of the Cells in the Lymph Stream of the Rabbit, *Bull. Johns Hopkins Hosp.* **40**:39, 1927.

3. Forkner, C. E.: Material from Lymph Nodes: IV. The Heterology of Lymphoid Tissue with Special Reference to the Monocyte-Supravital Studies, *J. Exper. Med.* **49**:323, 1929.

4. Opie, E. L.: Inflammation, *Arch. Int. Med.* **5**:541 (June) 1910.

into the subcutaneous tissue of the leg of a guinea-pig, Bezançon and Labbé<sup>5</sup> found that the afferent lymphatic vessels were dilated and contained many polymorphonuclear cells.

The object of the present investigation was to study the leukocyte content of lymphatic vessels draining a relatively small area into which a sterile inflammatory irritant had been previously injected.

#### METHOD

The experimental procedure employed was as follows: 3 cc. of a sterile inflammatory irritant was injected subcutaneously into the extensor surface of one of the forelegs of a rabbit, about 2 or 3 cm. from the shoulder joint. The irritant used was either infusion broth containing neither salts nor peptone and concentrated to one tenth of its original volume<sup>6</sup> or else a 0.5 per cent saline solution containing 5 per cent aleuronat and 3 per cent starch.

After varying periods ranging from eighteen to forty-eight hours, the animal was anesthetized with ether. The lymph was obtained by a method recently devised by Freund and Whitney, and adequately described by these authors elsewhere.<sup>7</sup> In brief, the method was as follows: The skin was incised below and parallel to the clavicle. The pectoral muscles were severed and the subclavian vein was exposed. Alongside of this vein and crossing it, usually at its distal end, an efferent lymphatic vessel was seen. Cannulation was performed by means of a capillary pipet. At its distal end and slightly below the subclavian vein, the efferent vessel connects with an axillary lymph node in which two or three small afferent lymph vessels may be seen to terminate. The afferent channels could also occasionally be cannulated. The leukocyte picture in the lymphatic vessel of the opposite side of the animal was often used as a normal control over the observations on the inflammatory side.

To prove that the channels studied were the tributary lymphatics and were therefore draining the area of inflammation, a 1 per cent trypan blue solution in physiologic solution of sodium chloride was injected subcutaneously at the site where the inflammatory irritant was usually injected. From twenty to thirty minutes later the regional lymphatic vessels and lymph node displayed the dye prominently.

The leukocytes were studied by the supravital technic as described by Sabin.<sup>8</sup> Neutral red was the only dye used. The basophils, eosinophils and neutrophils were all grouped together as polymorphonuclears. The monocytes were distinguished from the clasmatoocytes by the "rosette" formation. To obtain the differential formula usually 200 cells were counted. In several experiments, histologic sections were also made of the inflamed area and of the regional lymph node.

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5. Bezançon and Labbé: *Arch. de méd. expér.* **10**:318, 1898; quoted by Opie (footnote 4).

6. Gay, F. P., and Morrison, L. F.: Clasmatoocytes and Resistance to Streptococcus Infection, *J. Infect. Dis.* **33**:338, 1923.

7. Freund, J., and Whitney, C. E.: Distribution of Antibodies in the Serum and Organs of Rabbits: III. Agglutinin Content of the Lymph and Tissue of the Liver and of the Lymph and Muscle of the Leg, *J. Immunol.* **16**:109, 1929.

8. Sabin, F. R.: Studies of Living Human Blood-Cells, *Bull. Johns Hopkins Hosp.* **34**:277, 1923.

## RESULTS

In several normal rabbits, the efferent lymphatic vessel was cannulated and its cellular content was studied. Table 1 shows that in the normal efferent lymphatic vessel, the cells were practically all of the lymphocyte type. Only rarely an occasional monocyte was found. It

TABLE 1.—*The Leukocyte Picture in an Efferent Lymphatic Vessel in Normal Rabbits*

Rabbit	Absolute Number of Leukocytes per Cu. Mm.	Percentage of Polymorphonuclears	Percentage of Lymphocytes	Percentage of Monocytes	Percentage of Clasmatoocytes
1	11,300	0	100.0	0.0	0
2	55,000	0	100.0	0.0	0
3	15,000	0	100.0	0.0	0
4	9,000	0	100.0	0.0	0
5	21,000	0	100.0	0.0	0
6	14,400	.	.....	...	.
7	12,000	.	.....	...	.
8	.....	0	99.5	0.5	0
9	.....	0	100.0	0.0	0
10	17,500	0	99.5	0.5	0
11	14,000	0	100.0	0.0	0
12	.....	0	100.0	0.0	0

TABLE 2.—*The Leukocyte Picture in an Efferent Lymphatic Vessel in the Region of Local Inflammation*

Inflammatory Irritant	Rabbit	Hours After Injection of Irritant	Absolute Number of Leukocytes per Cu. Mm.	Percentage of Polymorphonuclears	Percentage of Lymphocytes	Percentage of Monocytes	Percentage of Clasmatoocytes
Infusion broth (concentrated)	14	18	17,000	15.5	83.0	0.0	1.5
	12	18	.....	8.0	90.0	0.5	1.5
	9	19	.....	1.5	98.0	0.5	0.0
	10	20	... ..	11.5	79.5	2.5	6.5
	8	22	.....	5.0	92.0	2.0	1.0
	11	23	.....	11.0	85.0	1.0	0.0
	15	46	.....	4.5	95.5	0.0	0.0
	13	48	6,200	6.5	90.5	1.5	1.5
Aleuro-nat	24	17	34,200	3.5	92.0	4.0	0.0
	20	18	.....	33.0	66.3	0.6	0.0
	27	18	10,000	16.0	83.5	0.5	0.0
	22	20	20,000	20.0	79.0	1.0	0.0
	17	21	5,750	3.3	96.6	0.0	0.0
	25	21	25,000	6.0	94.0	0.0	0
	23	21	25,700	7.5	92.5	0.0	0
	16	22	48,000	74.0	24.3	0.3	1.3
	21	23	24,750	17.0	83.0	0.0	0
	18	24	.....	36.3	63.2	0.5	0
	26	23	15,000	2.5	97.5	0.0	0
	19	49	.....	1.0	99.0	0.0	0

is noteworthy that this agreed with the observations of previous investigators, who examined lymph from other vessels. The absolute counts varied greatly, ranging from 9,000 to 55,000 leukocytes per cubic millimeter.

Table 2 reveals the leukocyte picture in an efferent regional lymphatic vessel as a response to a local inflammatory process. There was a definite qualitative change in the differential formula. Whereas normally polymorphonuclear cells were not found in the efferent lymphatic



vessel, a local inflammation caused by a sterile irritant revealed in each case the presence of polymorphonuclears. The percentage of these cells varied widely, ranging anywhere from 1 to 74 per cent. The significant point, however, was that the polymorphonuclear cells could always be found in the efferent lymph vessel when an inflammatory irritant had been previously injected. Other types of cells were not found so constantly, although, when the observations here were compared with the observations in normal animals, there seemed to be in some of the rabbits receiving the injections a tendency toward a slight increase in monocytes and clasmotocytes. The absolute numbers of leukocytes per cubic millimeter were too variable to permit any definite inference as to their possible significance.

#### COMMENT

This study clearly brings out the fact that a local inflammatory process produces a change in the differential leukocyte formula of a regional efferent lymphatic vessel. Polymorphonuclears, in varying proportions, always appear. Histologic sections of both the site of injection and the regional lymph node reveal an inflammatory process, showing that the inflammation extends at least as far as the regional lymph node. The presence of polymorphonuclear cells in the efferent lymphatic vessel indicates that at least some of these cells are returned from the inflamed region to the blood stream through the lymphatic channels.

#### SUMMARY AND CONCLUSIONS

The cellular content of an efferent lymphatic vessel of one of the axillary lymph nodes of the foreleg of a normal rabbit consists almost entirely of lymphocytes.

When local inflammation is produced by a sterile irritant, polymorphonuclears appear in the efferent lymphatic vessel of the regional lymph node.

Local inflammation after from eighteen to forty-eight hours often causes the monocytes and clasmotocytes to increase in number in the efferent lymphatic vessels; but this increase is not so constant as the presence of polymorphonuclears.

The inflammatory reaction involves both the site of the injection and the regional lymph node.

The polymorphonuclear leukocytes that migrate from the blood vessels into the inflamed area return, in part, to the blood stream by way of the lymphatics.

# Laboratory Methods and Technical Notes

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## AN IMPROVED RACK FOR STERILIZING VACCINES\*

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Sterilization of bacterial suspensions by submerging the test tubes or bottles containing them in a water bath at 60 C. is the usual method in many laboratories. If the amount of bacterial suspension in the container is small, it is difficult to keep it submerged so as to have the water in the bath well above the fluid level of the vaccine suspension. The rack here described was designed to meet this requirement.

It consists of a circular, perforated, heavy metal base, *A*, mounted on legs (fig. 1). Two upright metal rods, *C* and *D*, are fixed to it. A second copper disk, *B*, with six holes, each large enough to accomodate a vaccine bottle of 30 cc. capacity, is attached at a distance 1 cm. above the disk *A*. A third movable metal disk, *E*, slides up and down on the rods *C* and *D*. It has six circular holes in it, so fashioned that each will fit over the neck of a vaccine bottle of 30 cc. capacity. Two set screws, *F* and *G*, secure the disk *E* in the position desired. There is a perforated slot, *K*, for holding a thermometer, soldered into the center of the disk *E*. The largest diameter of the rack is 13 cm. and its height is 16 cm.

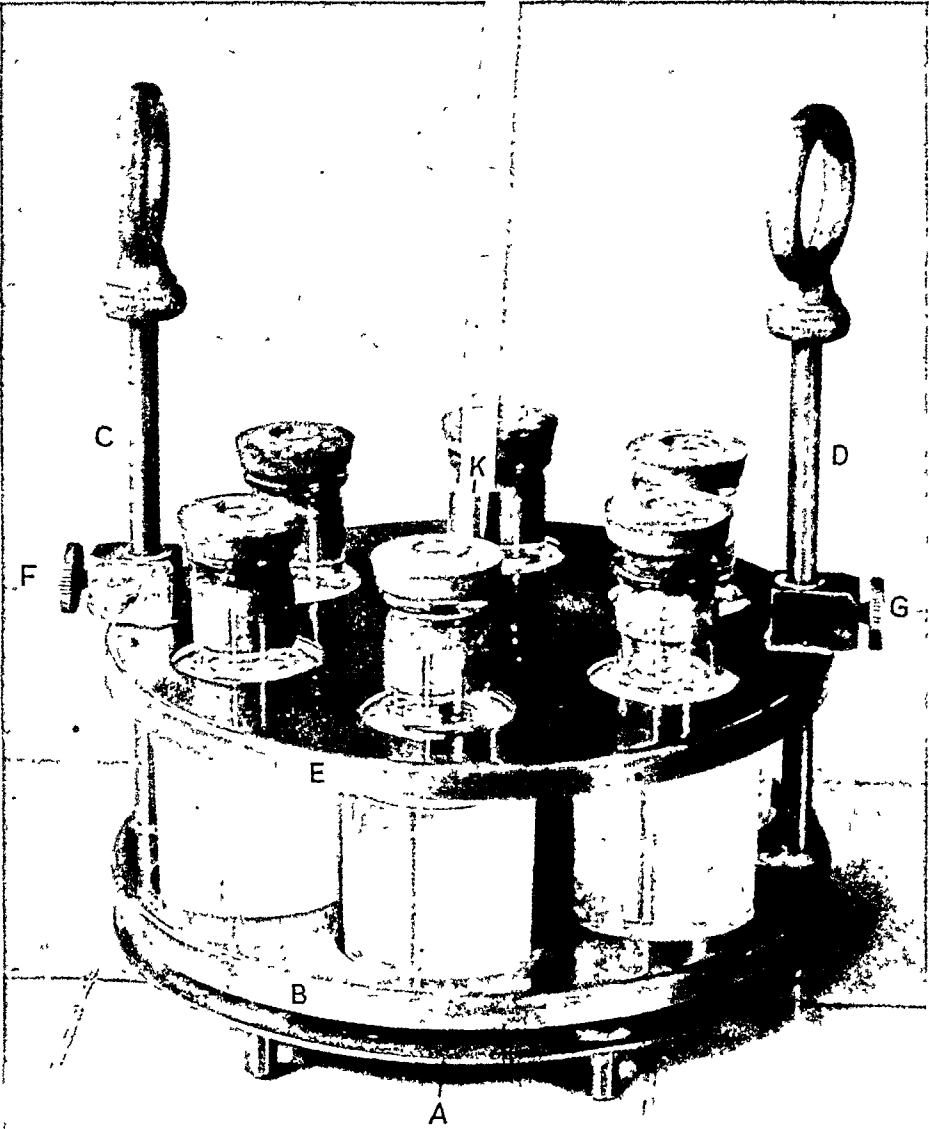
The bacterial suspension is placed in a vaccine bottle of 30 cc. capacity and this is stoppered with a sterile rubber cap. The disk *E* is brought down securely over the neck of the bottle and fixed in position by means of the set screws *F* and *G*. A thermometer is inserted into the slot *K*, and the apparatus is placed in the water bath; the level of the water reaching up to the neck of the vaccine bottle, beyond the lower level of the rubber cap.

The rack is of simple construction. Any skilled coppersmith can build one. It is small enough that even the inner boiler of a rice cooker may be used as a satisfactory water bath. There is no floating up of the vaccine container; when placed in the water bath, it remains completely submerged and both vaccine suspension and container may be maintained at an even temperature.

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\* Submitted for publication, April 19, 1929.

\* From the Pathological Laboratories, Jefferson Medical College Hospital.



A rack for sterilizing bacterial suspensions.

## THE CELL-PLASMA RATIO\*

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It has long been recognized that marked variation occurs in the plasma content of the blood relative to its cell content both in health and in disease. In health, the most important factor in the variation is the ingestion of large quantities of fluid. In disease, the prime factor is hydremia associated with primary renal disease or circulatory failure or some condition in the tissues of the body involving the chemistry of colloids and crystalloids. Indirectly, there is a relative increase in the plasma in primary and most secondary anemias, in which the number of the red blood cells is markedly reduced.

In any type of anemia and more particularly in anemia due to hemorrhage, periodic study of the cell-plasma ratio may be of value in the differential diagnosis and as a check on the therapy. The study of the cell-plasma ratio has led, moreover, to a more precise method for the estimation of hemoglobin, as will be described in another part.

### METHOD

1. Shake a few grains of dry powdered sodium citrate into a clean, dry capillary glass tube having an inside diameter of 4 mm. and a length of 10 cm.<sup>1</sup>

2. Holding the tube in the horizontal position or with the distal end slightly depressed, apply the proximal end to a bleeding puncture wound. A rapid, deep, incised wound of the finger made with a sharp lancet-headed needle will fill at least three such tubes with little or no pressure on the finger.

3. Fill the tube about two-thirds full, and mix the blood with the citrate by alternately elevating and depressing one end.

4. Allow the blood to gravitate to one end, seal that end with a plug of paraffin and place a broad rubber band snugly around the length of the tube, thus sealing both ends. It is well to file off the cut edges to avoid injury to the finger or tearing of the rubber band.

5. Centrifugate at high speed (plugged end down) for a sufficient length of time to secure the maximal separation of cells and plasma. This is determined as the length of time after which repeated centrifugation no longer diminishes the length of the cell column. Once established, the same button on the rheostat and the same period of time may be used with every specimen.

6. Measure the cell column and the plasma column with a millimeter rule, and determine the percentage of each (e. g., 30 mm. of plasma and 30 mm. of cells are equivalent to plasma 50 per cent and cells 50 per cent or a cell-plasma ratio of  $\left(\frac{c}{p}\right) 1$ ).

*Method Using Venous Blood Compared with Method Using Capillary Blood.*—Contrary to expectations, it was found that little difference obtained in the results

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\* Submitted for publication, April 26, 1929.

\* From the Laboratory of St. Bartholomew's Hospital.

1. Felsen, J.: A Simple Method of Testing for Blood Compatibility, Arch. Path. 4:552 (Oct.) 1927.

whether capillary or venous blood was used. Even prolonged and marked pressure on a bleeding digit elicited only a slight error. Prolonged application of a tourniquet, however, made a small but definite error in the case of venous blood.

*Method Using Capillary Tube as Container Compared with Method Using Centrifuge Tube.*—A check was then made against the 15 cc. graduated centrifuge tube. It was found that the thickness of the column of blood in the centrifuge tube increased the inaccuracy of the reading many times as compared with the slender column in a capillary tube. With the exercise of great care, however, the readings were comparable. Thus, repeated reading in a case of polycythemia vera gave plasma 31 per cent and cells 69 per cent for the capillary tube and plasma 40 per cent and cells 60 per cent for the centrifuge tube.

#### APPLICATION OF METHOD

As it had been determined in a series of 500 cases that in the hands of different technicians the cell plasma values of venous and of capillary blood were comparable, capillary blood alone was used, except in isolated instances.

*Variations in the Normal Person.*—It was found that in the normal person great variation occurred in the proportion of plasma to cells. This was most marked within the first half hour after ingestion of large amounts of fluid, the relative plasma value then being high, and in starvation, the relative plasma value then being low. The influence of fluids was so marked that one could almost trace the rate of the water-absorption by periodic determinations of the cell-plasma ratio. Constant values in any one person were found under basal conditions (fourteen hours' fast and rest in bed). The average value of the plasma in the blood from a healthy man or woman under basal conditions was from 45 to 55 per cent and the average value of the cell-plasma ratio was 1 or a little less than 1. That is, the plasma column was nearly always slightly longer than the cell column. The value of the cell-plasma ratio ( $\frac{c}{p}$ ) was obtained by dividing the percentage of cells in the column of centrifugated blood by the percentage of plasma. Excessive sweating and exercise tended to increase the ratio in almost direct proportion to their intensity and duration.

*Variations in Persons Presenting Pathologic Conditions.*—Severe secondary types of anemia, especially those associated with hemorrhage (e. g., duodenal ulcer), primary anemias, severe diabetes and nephritis with water retention show a relative increase in plasma content and, therefore, a cell-plasma ratio of much less than 1. In cases of bleeding gastric or duodenal ulcer, the ratio is lowest within the primary post-hemorrhagic period when the vessels are being rapidly filled with fluid. The ratio slowly rises, approaching 1 as the cells are regenerated. It is a more reliable index of the progress of a bleeding lesion than the percentage of hemoglobin and the blood count. Persistent loss of blood is accompanied by a low ratio, which is proportionate in a measure to

the duration and severity of the hemorrhage. Table 1, showing the determinations of the cell-plasma ratio in a case of bleeding gastric ulcer, illustrates this point. Autopsy disclosed extensive ulcerations of the prepyloric region with evidence of a recently plugged vessel of moderate size in the floor of one ulcer. The wall of this ulcer also showed early carcinomatous changes.

TABLE 1.—*Comparison of the Percentage of Hemoglobin and Number of Red Cells with the Cell-Plasma Ratio in a Case of Hemorrhage from Duodenal Ulcers*

Date	Hemoglobin, per Cent	Red Cell Count	Cell-Plasma Ratio	Remarks
8/ 8/28.....	74	3,850,000	0.31	
8/10/28.....	..	.....	0.50	96 hours after hemorrhage
8/11/28.....	69	.....	0.40	
8/13/28.....	58	3,200,000	0.20	Hemorrhage
8/14/28.....	..	.....	0.15	
8/23/28.....	56	3,680,000	0.42	
9/ 4/28.....	50	3,000,000	0.26	
9/11/28.....	..	.....	0.50	1 hour before death

TABLE 2.—*Effect of a Blood Transfusion on the Cell-Plasma Ratio in a Case of Hemorrhage from Duodenal Ulcers*

Date	Cell-Plasma Ratio	Remarks
8/16/28.....	0.30	A few minutes before a transfusion of 1,000 cc. of blood (direct method)
8/16/28.....	0.20	Five minutes after the transfusion
8/17/28.....	0.31	Twenty-four hours after the transfusion
8/18/28.....	0.26	Forty-eight hours after the transfusion

TABLE 3.—*Comparison of the Percentage of Hemoglobin and Number of Red Cells with the Cell-Plasma Ratio in a Case of Duodenal Ulcer*

Date	Hemoglobin, per Cent	Red Cell Count	Cell-Plasma Ratio	Remarks
10/ 3/28.....	80	5,210,000	0.75	Before dinner
10/ 6/28.....	80	4,410,000	0.85	Before dinner
10/ 7/28.....	..	.....	0.26	Gastro-enterostomy 1 hour after hypodermoclysis and 5 minutes before a transfusion (1,000 cc. by direct method)
10/ 7/28.....	..	.....	1.2	Ten minutes after the transfusion
10/16/28.....	..	.....	1.5	
10/16/28.....	..	.....	1.0	Taken shortly after dinner
3/11/29.....	72	4,000,000	0.39	Taken before breakfast

A transfusion in the same case is interesting in that it caused no considerable change in the ratio for at least forty-eight hours (table 2).

Another patient studied over a longer period showed somewhat different results (table 3). This patient was a woman of the thin, scrawny, dehydrated type, who had a duodenal ulcer. The high values of the cell-plasma ratio in this case were probably associated with dehydration, which was possibly due to the short circuiting of the gastric contents.

At the time of the last estimation, the patient had returned to the hospital because of an adherent gallbladder which had perforated and ruptured into the stomach. The transfusion in this case had changed the proportion from cells 21 per cent and plasma 79 per cent to cells 58 per cent and plasma 42 per cent. It suggests the rapidity with which fluids may pass from within blood vessels to dehydrated tissues.

The healthy donor who had been used for the transfusion showed no change in the cell-plasma ratio. This was probably due to the rapidity of the withdrawal of blood, and indicates that in the loss of blood by mechanical means without associated shock it takes some time for the body fluids to attempt to make up the loss of fluid. Clinically, the average healthy donor rarely experiences thirst after a transfusion of moderate size. It is not at all unlikely that in a robust person such a transfusion causes little disturbance in the fluid balance.

In marasmus, cachexia and all other states associated with dehydration, the cell-plasma ratio is high owing to the relative concentration of the cellular elements.

In chlorosis and polycythemia there is an absolute increase in the number of erythrocytes and a resulting high cell-plasma ratio. This is illustrated in a case of polycythemia in which the percentage of the hemoglobin was 110, the number of the red cells 7,040,000 and the cell-plasma ratio 1.5.

#### SUMMARY

The cell-plasma ratio affords a simple index to the relative concentration of cells and plasma in the blood.

Some normal and pathologic variations have been described.

The practical application of this method in the study of hemorrhagic states has been illustrated.

## General Review

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### RECENT WORK ON THE EFFECTS OF INANITION AND MALNUTRITION ON GROWTH AND STRUCTURE

C. M. JACKSON, M.D.

MINNEAPOLIS

(Concluded from page 1078)

*Effects of a Deficiency of Vitamin E. (Antisterility).*—The existence of a fat-soluble antisterility vitamin E may be regarded as definitely established through the pioneer work of Evans and his associates, confirmed by Sure (1924, 1926, 1926a, 1926b), Mattill and his associates (1924, 1926, 1927), Daniels and Hutton (1925), Mason (1925, 1926), Beard (1926), Kennedy (1926), Tso (1927) and Suzuki and his co-workers (1928). Some skepticism, however, has been expressed, especially by Hogan and Harshaw (1924), Nelson and his associates (1926) and Hartwell (1926). In reviewing the question, Kennedy (1926a) concluded that "as yet it has hardly emerged from controversy, but it is impossible to deny that the evidence in its favor is very strong."

The earlier papers by Evans and Bishop, announcing the discovery of the antisterility vitamin, were reviewed in my previous work (Jackson, 1925). Evans and Burr (1925), Evans (1925) and Evans, Burr and Althausen (1927) presented more detailed evidence that rats reared on various synthetic mixtures of protein, fat, carbohydrate, salts and vitamins (A, B and D) grow well but exhibit sterility unless the diet is supplemented by vitamin E. According to Beard (1926), a similar factor is apparently necessary for normal reproduction in the mouse. A possible relationship between the antisterility vitamin E and the assimilation of iron was suggested by Hart and his co-workers (1925) and Simmonds, Becker and McCollum (1927). Recently (1928), however, the latter authors withdrew this suggestion. The character of the sterility is different in the two sexes, which must therefore be considered separately. Evans (1928b) recently showed that the maximum body weight attained is distinctly higher in rats of both sexes when vitamin E is adequately supplied. Bisceglie (1928) found that deficiency of vitamin E in rats results in histologic changes (interpreted as hyperfunctional) in the thyroid, suprarenal and hypophysis.

*Reproduction in the Male (Sterility):* While the earlier investigation was devoted chiefly to the effects in the female rats, Evans and Bishop (*J. A. M. A.* 81:889, 1923) noted that the spermatozoa also



are injured and eventually destroyed by the deficiency of vitamin E. Mattill and associates (1924, 1926) observed that in male rats, over 100 days old, on diets deficient in vitamin E, there is a decline in procreative power, associated with progressive degeneration of the testis. In advanced stages, the testis is from 40 to 70 per cent subnormal in weight. The sperm cells and the lumen of the seminiferous tubules disappear, but the interstitial tissue proliferates. After the animals are 5 months of age, the recovery of the degenerated testis on the administration of vitamin E is rarely possible.

The histologic effects of a deficiency of vitamin E on the testis of the rat were studied in detail by Mason (1925, 1926). After the rats had been from three to five months on a diet deficient in vitamin E (beginning at weaning), the weights of the testes averaged only 44 per cent of normal. Degeneration began in from fifty to sixty-five days, and was practically complete after 100 days. The stages of degeneration in the seminiferous tubules were: (1) clumping of the spermatozoa, which became detached in irregular masses; (2) disappearance of the spermatozoa in most tubules, and karyorrhexis of the spermatids, with disappearance of the cell walls; (3) formation of multinucleated giant cells by fusion of the degenerated spermatids, with a beginning degeneration also in the spermatocytes; (4) presence of a few remaining giant cells, with the spermatocytes and the spermatogonia in various stages of necrosis; (5) reduction of the germinal epithelium to a syncytial layer of Sertoli's cells in the periphery of the shrunk tubules, with the interstitial cells not degenerated, and the epithelium in the ducts of the epididymis showing fatty degeneration in extreme cases.

The destruction of the male germ cells, and eventually of the entire seminiferous epithelium, was also noted by Evans (1925), Evans and Burr (1925) and Suzuki and his associates (1928). The process was described fully in a recent monograph by Evans, Burr and Althausen (1927). They recognized the following stages of sterility: (1) a short period during which the spermatozoa (from the vaginal plug) appear normal in number, morphology and motility, but have already lost their fertilizing power; (2) a period similar to stage 1, but with loss of motility by the spermatozoa; (3) a period similar to stage 2, except for the appearance of isolated groups of spermatozoa, together with attached Sertoli's cells; (4) disappearance of sperm from the plug; (5) loss of power to form the plug, with preservation of some sex interest, and (6) loss of all sex interest. In late stages of sterility, with normal body weight (about 400 Gm.), the testes are only about one-third normal weight, and are pigmented and watery in structure. Histologically, the tubules show a progressive (to total or nearly complete) loss of seminiferous epithelium, as described by Mason.

While the interstitial (Leydig) cells apparently remain normal, there may be an increase in connective tissue macrophages, associated with phagocytic resorption of the degenerated seminiferous epithelium. The testes of males of the second or succeeding generations on the deficient diets degenerate earlier than those of males of the first generation. On the feeding of a curative diet containing vitamin E, recovery of the normal structure by regeneration from islands of resistant germinal epithelium is possible, but may be attained in only one fourth of the cases, even when the curative diet is fed as soon as the sterility appears. Tubules reduced to Sertoli's cells only are apparently unable to regenerate and persist unchanged.

The effects of a deficiency of vitamin E on the testis appear, in general, similar to those previously described by many investigators as occurring in various forms of partial or total inanition. In some cases, in the earlier experiments, the effects observed may have been due to an unrecognized associated deficiency of vitamin E. Mattill (1927) and Evans (1928a) presented evidence indicating that in rats a deficiency of vitamin B (which has been considered especially harmful to the testis) rarely causes testicular degeneration when vitamin E is adequately provided.

**Reproduction in the Female (Sterility):** It is most remarkable that while a deficiency of vitamin E causes sterility also in the female, the process is radically different from that in the male. Recent work by Mattill, Carman and Clayton (1924), Mason (1925), Evans and Burr (1925) and Suzuki and his associates (1928) strongly confirmed the original discovery by Evans and Bishop that in the female rat during a deficiency of vitamin E the ovary and ovulation, fertilization and implantation remain unimpaired, but sterility occurs through resorption of the implanted embryos. Bisceglie (1928) alone found a profound degeneration of the ovarian follicles.

The process was recently described in detail in the excellent monograph by Evans, Burr and Althausen (1927). Their extensive and carefully controlled observations revealed nothing abnormal occurring during the period of deprivation of vitamin E until the eighth day of gestation. From that time, retardation and abnormality of embryonic development became progressively evident until the death of the fetuses, about the thirteenth day, followed by rapid fetal and (later) placental resorption. The embryos showed subnormal development, which affected especially the mesodermal derivatives. The yolk sac showed a reduced size and a smaller number of entodermal villi and of mesodermal blood islands. The outgrowth and differentiation of the allantois were impaired. The maternal placenta was reduced in size but was nearly normal in structure. It continued to grow for several days after the fetal death, but was later resorbed. Early fetal death followed

subnormality of the yolk sac; later death followed injury of the allantois. The hematopoietic organs of the embryo were reduced, and the entodermal anlage of the liver was often subnormal. There was a striking reduction in the number of blood cells in the embryonic vascular system. The anemia and subnormal development of the yolk sac and allantois probably resulted in fetal death through starvation and asphyxia.

About two months were required to exhaust the stored vitamin E of female rats that previously had been on normal diet. When females were reared from weaning time on diet free from vitamin E, enough of the vitamin might be retained to permit one normal gestation (rarely more). While a lack of vitamin E caused female sterility, an excess of the vitamin did not increase either the normal number of young in a litter or the average weight at birth.

Even on normal diets, however, resorption occurred in about 7 per cent of the embryos. Barry (*Carnegie Contrib. Embryol.* no. 53, 1920) observed fetal resorption resulting also from the starvation of pregnant rats. It therefore appears doubtful whether the contention is justified that fetal resorption occurs only from the deficiency of vitamin E. In most cases, however, female malnutritional sterility is undoubtedly brought about through a suppression of ovulation rather than through a disturbance of the process of gestation.

While a deficiency of vitamin E apparently causes anemia in the embryo, Kohls and Evans (1928) did not find evidence that it produces anemia in adult rats. Bishop and Morgan (1928) observed the spontaneous occurrence of multiple deciduomas in the uterus of a rat on a diet deficient in vitamins A and E.

Lactation: Simmonds (1924) and other investigators found difficulty in rearing young rats through the nursing period when the mothers were placed on many natural or synthetic diets apparently containing all the necessary nutritional factors. Evans (1924) noted that even with the inclusion of vitamin X (E), the food requirements for lactation were not fulfilled. The question was recently discussed by Tso (1927) and Evans and Burr (1927a, 1928a). One view (now well established) is that the process of lactation requires an enormous increase in some of the known dietary factors, as was shown by Simmonds for protein and by Sure, Evans and Burr, and others for the requirement of vitamin B during this period. The other possibility is that certain natural foods contain some more specific galactagogue factor that has not yet been demonstrated.

Paralysis of the Young: As was recently shown by Evans and Burr (1928a), when mother rats are on diets deficient in vitamin E, the young appear to grow normally during the lactation period, but nearly three fourths of them develop a partial paralysis. This is frequently

noted a day or two before weaning and becomes progressively severe during the next four or five days. The musculature of the body wall is affected, so that the rats are unable to right themselves when placed on their backs. The hind limbs present a spastic paralysis, in some cases preceded by flaccid paralysis, with dragging of the limbs. About 35 per cent of the affected animals die, 17 per cent (mild cases) recover fully, and 48 per cent continue paralyzed to a variable extent throughout life. After two or three months, many develop bilateral atrophic skin lesions with bare areas over the upper part of the thigh and the mid-dorsal region. The administration of vitamin E does not cure the paralysis after it is once well established, but some of the paralyzed females have later been able to become pregnant and give birth to normal young.

*Effects of a Deficiency of Recently Discovered Vitamins.*—As mentioned in the section on vitamin B, much evidence has accumulated, establishing beyond reasonable doubt the composite nature of this vitamin. As early as 1915, Funk and Macallum recognized the possibility of separable growth components in yeast. Mitchell (1919) reviewed the conflicting evidence as to the identity of the water-soluble growth-promoting vitamin and the antineuritic vitamin. McCollum and his associates formerly supported the view that the water-soluble B represents a single vitamin, but most of the more recent work has tended to confirm the theory that yeast (and some other carriers of vitamin B) contain at least two separable factors: the heat-labile antineuritic (anti-beriberi) vitamin and the heat-stable "growth-promoting" vitamin. The heat-stable factor appears somewhat similar to Wildiers "bios," or Funk's "vitamin D" (not to be confused with McCollum's antirachitic vitamin D), and is probably identical with Goldberger's antipellagra ("P-P") factor. Both of the component factors of B appear necessary for health and growth, and both are usually abundant in yeast. Wheat and maize germs seem to be relatively rich in the antineuritic vitamin, but poor in the antipellagra factor.

Experimental evidence for the composite nature of vitamin B has been presented by numerous investigators, including the following (using the rat or pigeon in most cases): Emmett and Luros (1920), Funk and Dubin (1921), Heaton (1922), Levene and Muhlfeld (1923), Smith and Hendrick (1926), Goldberger, Wheeler, Lillie and Rogers (1926), Goldberger and Lillie (1926), Hauge and Carrick (1926), Goldberger (1927) in human pellagra, Salmon (1927), Salmon, Guerrant and Hays (1927), Chick and Roscoe (1927), Hassan and Drummond (1927), Sherman and Axtmayer (1927), Williams and Waterman (1927), Eddy (1927), Evans and Burr (1927a, 1928c), Kennedy and Palmer (1928), Findlay (1928), Black, Sassaman and Holaday (1928) and Hogan and Hunter (1928).

The nomenclature of the newly discovered vitamin factors is in a state of great confusion, as was recently well shown by Smith (1928). Shall the term vitamin B be abandoned (as suggested by Sherman), or retained merely in the old, composite sense (Salmon, Smith) or restricted to designate only one of the newly recognized factors? To retain the term vitamin B in the composite sense would be contrary to precedent in the case of vitamin A, which originally meant the composite fat-soluble vitamin, but was later restricted by excluding the antirachitic factor (D). The proposal of the British Committee on Accessory Food Factors to use B<sub>1</sub> for the thermolabile (antineuritic) factor and B<sub>2</sub> for the thermostabile factor is likewise open to serious objections, as noted by Smith (1928) and Dutcher (1928).

If the term vitamin B is in the future to be restricted to one of the component factors, which shall it be? Chick and Roscoe suggested vitamin B *sensu stricto* to designate the "growth promoting," or anti-pellagra, factor. This appears undesirable, since beriberi and polyneuritis have been so long and so prominently associated with a deficiency of vitamin B. Growth, on the contrary, is a more generalized function, dependent on more than a single vitamin; and the probable relationship of the second B factor to pellagra has been only recently recognized. It would therefore seem more logical and more satisfactory to retain the term vitamin B in the restricted sense of the antineuritic factor, in accordance with the usage of Goldberger and others, and contrary to the proposal of Sherman and Smith. This plan is supported by McCollum (Dutcher, 1928) and by Hogan and Hunter (1928).

If vitamin B is to mean the antineuritic vitamin, what term shall be adopted to designate the second B factor? The term "growth-promoting" has been frequently used for this factor, but it appears inappropriate, since both B factors (as well as other vitamins) are essential for growth. Salmon proposed "B-P" factor for the antineuritic, and "P-P" (Goldberger's pellagra-preventing) for the second factor. Sherman suggested "vitamin F" for the antineuritic factor and "vitamin G" for the growth-promoting or antipellagra factor ("P-P"). But if vitamin B is to be retained for the antineuritic factor, it seems more logical (as proposed by Hogan and Hunter) to use "vitamin F" for the second growth-promoting factor, which appears to be closely related to (if not identical with) Goldberger's pellagra-preventing ("P-P") factor. Evans and Burr (1927a, 1928b), recently suggested the term "vitamin F" to designate another growth-promoting dietary factor, to be discussed later. This factor might instead be termed "vitamin G," if the newly discovered vitamins are (as in the past) to be designated by the letters of the alphabet in approximate order of discovery.

As to the effects of a dietary deficiency of the second, growth-promoting (or antipellagra) factor, most of the investigators noted merely a failure of growth in young animals. Young rats on diets thus deficient, as a rule, soon cease to grow, and after a variable period of nearly stationary weight, usually show a progressive emaciation with a decline in weight, and die from malnutrition without any external evidence of special lesions. In certain cases, however, especially of older animals subjected to experiment for long periods, characteristic disturbances of the skin and other symptoms suggestive of pellagra have been observed.

Antipellagra Factor (P-P), B<sub>2</sub> or Vitamin F: Credit for the discovery of the antipellagra factor is due chiefly to Goldberger and his associates. Continued work in this field led Goldberger to abandon his former theory that pellagra is caused by a dietary deficiency of protein. "Summing up," he wrote in 1926, "it may be stated that the available evidence seems to leave no reasonable doubt but that pellagra is caused by a faulty diet. The primary dietary fault appears to be of the nature of a deficiency of a factor P-P, very probably but not certainly identical with a dietary essential heretofore included with the anti-neuritic under the designation 'vitamin B,' which some workers have attempted to identify with bios." Goldberger (1927) described the distribution of this heat-stable factor in various foodstuffs (it is especially abundant in yeast and lean meat), and concluded that in pellagra in man "this deficiency arises when the diet does not include enough of the foods which carry the vitamin P-P to supply the needs of the body for this food factor."

This factor P-P ("pellagra-preventing") was first recognized by Goldberger and Tanner (1925) in dietary experiments with pellagra in man. Further experiments on animals were reported by Goldberger and Lillie (1926). When young rats were fed a diet apparently complete except for the antipellagra factor, growth was soon arrested, but symptoms of polyneuritis did not occur even when the experiment continued far beyond the period when such symptoms appear during a deficiency of vitamin B. Many of these rats ultimately developed symptoms of ophthalmia and pellagra-like lesions of the skin. There was a variable loss of fur, usually beginning on the head, neck or shoulder. The depilation sometimes extended to an almost complete denudation of the head, neck and trunk. The denuded areas were often sharply delimited and were bilaterally symmetrical. Either with or without such loss of fur, some rats developed a dermatitis with bilaterally symmetrical lesions of the ears, the front of the neck and the chest or the limbs (paws). The shortest period within which this dermatitis appeared was about seven weeks. A few rats showed ulcerative lesions at the angles of the mouth or the tip of the tongue.

Mouriquand (1926) observed a pellagra-like syndrome in guinea-pigs fed on maize or the ordinary ration with the omission of grass. The disorder was characterized by loss of hair, intestinal troubles and general dystrophy. The exact nature of the deficiency responsible for the condition was uncertain.

A somewhat similar pellagral disorder was produced by Scheunert and Lindner (1927) in albino rats on a diet containing too little vitamin B. These investigators were apparently unaware of the recent work by Goldberger and others in this field, and did not recognize the possibility of different factors in the vitamin B complex. It may be assumed, however, that their results (skin lesions) were probably due to a deficiency of the antipellagra (P-P) component. These lesions (which appeared in all their rats on the diet deficient in B over fifty days) began in the region of the eyes, with conjunctivitis, dermal hyperemia and depilation. Simultaneously, papillary outgrowths (not mite infection!) appeared around the nasal and oral apertures. On the limbs, especially the dorsum of the feet, there occurred similarly bilateral hyperemia, depilation, and epidermal desquamation with a copious exudate. Histologic sections sometimes showed also a slight cellular infiltration of the subcutaneous region. In general, the condition was considered as equivalent to pellagra in man.

The work of Chick and Roscoe (1927, 1928) directly confirmed the conclusions of Goldberger as to the effects of a deficiency of the antipellagra (P-P) factor. Their rats with pellagra usually maintained their weights and were active, though in poor condition. The urine often appeared slightly blood stained. The hair coat was rough and the hair dropped out in patches, leaving inflamed areas on the nose (sometimes on the ears) and on the backs of the forepaws. These areas were often edematous and tended to enlarge and spread around the nose and the mouth, the thorax, and the hind limbs. There was marked conjunctivitis. The rats continued two or three weeks in this condition before death occurred. The postmortem examination did not reveal any further abnormality, aside from an "unhealthy condition" of the whole alimentary tract. Especially the small intestine was inflamed and atrophic, containing bloodstained mucus.

Salmon (1927) likewise noted in rats on seed diets deficient in the growth-promoting factor of vitamin B "a tendency to lose their fur in patches and in a few cases to develop an inflammation of the eye." These were probably symptoms of the same pellagral disorder.

Findlay (1928) recently described the pellagra-like lesions in rats on diets deficient in vitamin F ( $B_2$ ), confirming the results of Goldberger and his associates. He obtained the failure of growth with the characteristic lesions of the skin, oral mucosa, tongue and eyes, followed by death in two or three weeks. The liver, spleen, thymus and testes

were markedly subnormal in weight, the kidney nearly normal and the suprarenal glands above normal. Aside from those in the skin and the nervous system, the histologic changes in general resembled those of simple inanition. A papillomatous lesion found in the cardiac portion of the gastric mucosa was thought to be nonspecific for the deficiency of the vitamin.

The possible relation of pellagra to the "black-tongue" syndrome of dogs has received considerable attention. Underhill and Mendel (1925) concluded that the Chittenden-Underhill pellagra-like syndrome in dogs may be due to the lack of an unrecognized vitamin present in carrots and butter fat. Goldberger and his associates (1926, 1928) believed that their experimental pellagra in dogs was probably identical with the Chittenden-Underhill syndrome. The condition developed slowly, with a progressive stomatitis and variable lesions on the cheeks and tongue. Constipation was frequent, and was sometimes succeeded by final diarrhea (sometimes bloody). In from 40 to 50 per cent of the males, there was an area of pellagra-like eruption in the skin of the scrotal region; this area was reddened and sometimes pigmented, with desquamation. Lacrimation, convulsions and other symptoms were noted in a few cases. Occasional lesions of the alimentary or respiratory tract were observed at necropsy. Denton (1928) found the lesions in these animals similar to those of pellagra in man.

Denton (1925) made a thorough study of the pathologic changes of pellagra in man, based on sixteen cases in Panama. The essential clinical symptoms included the characteristic lesions of the skin, mouth and tongue, gastro-intestinal disturbances and symptoms referable to the central nervous system. "Pellagra is a disease in which the lesions are confined to epithelial surfaces without extension to deeper tissues or organs." The cutaneous lesions involved the following stages: injury, or the fibrolytic stage; reaction, or the dermatitic stage; repair; compensatory vascular ectasia, or the erythematous stage; the cicatricial, or atrophic stage. The brownish-red color of the oral and esophageal mucosae (with or without necrotic lesions), dark-red small intestine and variable degrees of colitis were gross characteristics. Most of the viscera did not show constant or important lesions. Variable degeneration (tigrolysis) of the nerve cells in the central nervous system was observed.

Sutton (1926) reported observations in fifty-six cases of pellagra, in five of which necropsies were recorded. The "unknown toxin" of pellagra attacked chiefly the ectodermal structures of the skin, the alimentary tract and the central nervous system, resulting in the familiar diagnostic tripod of dermatitis, diarrhea and dementia. The lesions of the skin and of the oral mucosa were described by Sutton in detail. At necropsy, there appeared atrophy and thinning of the alimentary canal,



with hyperemia and ulceration of the oral mucosa and lower bowel. Abnormal pigmentation was found in the ganglionic cells, heart muscle, liver and spleen. Atrophy of the lateral and (sometimes) posterior columns of the spinal cord was noted. Sutton did not accept Goldberger's theory that pellagra is caused by a deficiency of protein; he inclined toward the theory that it is caused by a toxin. Crutchfield (1928) studied especially the skin and mucosa in 109 cases with ten autopsies.

Klauder and Winkelman (1928) described the symptoms and other pathologic manifestations of pellagra in chronic alcoholic addicts, who seem especially predisposed to this disorder. The characteristic degeneration of the brain cells was observed by the Nissl method.

Other Vitamins (Vitamin G): Evans and Burr (1927a) observed that a highly purified diet of casein, sucrose and salts was not adequate for normal growth and ovulation in rats, even when this diet was supplemented by foods containing high levels of the vitamins A to E, inclusive. Since the deficiencies of growth and ovulation were corrected by the addition of small amounts of lettuce, liver or lard, it was concluded that these substances probably include a hitherto unrecognized factor of growth, for which the name vitamin F or H was suggested. In a further study (1928b), they found that the addition of lard to this diet of sugar and casein brought about better growth than did the addition of butter, coconut oil or corn oil; but that in supporting lactation the lard was the least effective of the three. Burr (1928) also discovered in rats on the diet of sugar and casein certain degenerative changes involving a necrosis of the tail. This disorder was prevented or cured by the addition of small doses of lard to the diet. If the term vitamin F is applied to the second B, or antipellagra, factor (as has been suggested) the new factor discovered by Evans and Burr seems the logical one for recognition as vitamin G.

McCay, Bing and Dilley (1928) described briefly the results of a feeding experiment on growing trout. A diet of purified rations (a mixture of casein, boiled starch and salt) proved inadequate, even when supplemented with all the known vitamins from A to E. The addition of raw liver resulted in excellent growth, however, and for the unknown factor in the liver they proposed the name "factor H." It seems quite possible that this factor may be identical with the new vitamin promoting growth discovered by Evans and Burr, for which the term vitamin G is now proposed.

It is not at all likely, however, that the list of vitamins is finally exhausted. Some or all of the vitamins now recognized are probably composite in character, and other undiscovered factors doubtless exist. Richardson, Palmer and Kennedy (1928) believed that the highly purified foods which they used, had been dispossessed of some unknown

substance that is essential for the utilization of fat by the body. It is indeed quite possible that before the knowledge of nutrition is complete all the letters of the alphabet will have been insufficient to designate the various vitamins and similar dietary factors involved.

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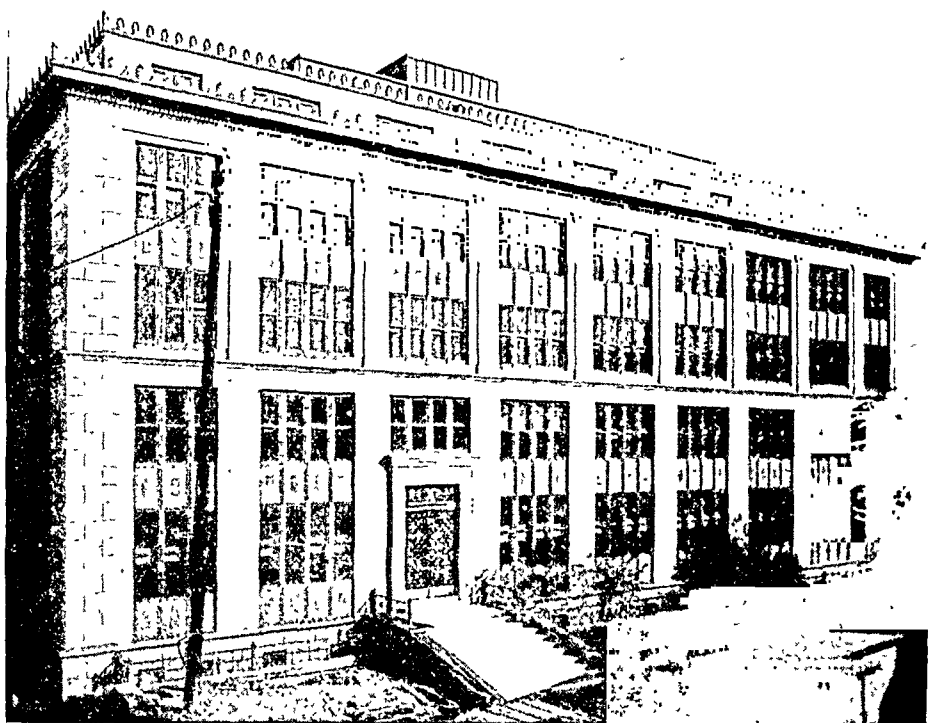
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## Notes and News

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**Dedication of Institute of Pathology, Western Reserve University.**  
—In the autumn of 1926 the General Education Board appropriated \$750,000 for the construction of an Institute of Pathology at Western Reserve University. After study of the situation it was decided that the building would house all the work in pathology of the university and the associated hospitals, including Lakeside Hospital, Babies' and Children's Hospital, Maternity Hospital and the Hanna Pavilion. It was further decided that the institute would serve as a central laboratory for the more intricate tests that deal with biochemistry, immunology and bacteriology. After careful consideration of similar buildings on this continent



Institute of Pathology, Western Reserve University.

and in Europe, plans were drawn by Abram Garfield of Cleveland. Ground was broken in February, 1928. The building was constructed by Crowell and Little of Cleveland, and was occupied in June, 1929.

The building is of buff brick and Indiana limestone. It consists of sub-basement, basement and five floors, the uppermost of which is for animal quarters. It is an oblong building, 160 by 60 feet, with steel framework, supported on forty steel columns. The sub-basement houses machine rooms and contains seven rooms for the storage of pathologic materials such as tissue blocks.

The basement contains a large museum which is designed so as to provide specimens for clinical teaching throughout the medical group. The morgue, chapel, undertakers' room, receiving room, living quarters for an orderly and stable for horses and sheep are found on this floor. An amphitheater runs through this floor and the first floor, projecting out over, and concealing, a ramp where delivery of bodies may be made under cover. The amphitheater contains 166 seats and has been given acoustic treatment.

The first floor is entirely for student purposes. The class room for pathologic histology has ample capacity for sixty-six students with an expansion capacity of ten more. A small auxilliary class room for demonstrations can accommodate fifty students. Communicating by dumb waiter with the museum preparation room below, is a room for the exhibition of gross morbid anatomic material. A room is provided for experimental work by the students. Student entrance to the amphitheater is from the first floor level. Locker rooms and toilets are provided for men and women students.

The second floor houses the departmental library, with a capacity of 10,000 volumes, stockrooms, a conference room, record rooms, nine rooms for staff with office and private laboratory facilities and a general experimental room for housing heavy apparatus. From this floor the staff can go down one flight to the class rooms or up one flight to the rooms for routine hospital work.

The third floor contains one office, a shop, a room for cleaning of glassware and preparation and sterilization of mediums, separate rooms for bacteriology, immunology and preparation of histologic material. Dental pathology has two large units on this floor. Biochemistry has four large units. There are three cubicles for investigators who come from outside the university group and these rooms share a common laboratory.

The fourth floor contains the general autopsy room with two tables, a private autopsy room with one table, and a preparation and store room between. The art suite combines a large room for the artist and a large room for gross and microscopic photography. A dark room serves the photographic room and an experimental x-ray room. There are eighteen rooms for members of clinical departments who wish to do research in subjects closely related to pathology. Sixteen of these are arranged in groups of four small rooms, with a common laboratory.

The fifth floor has a large space allotted to dogs, with built-in cages and a central open air court for exercise. Separate rooms are provided for rats and mice, birds and monkeys, rabbits and guinea-pigs, fish and frogs. There is a metabolism room for animals, a dark room for research with various types of light, an isolation room, a food storage and preparation room, a cage cleaning room, an inoculation room and a complete suite for surgical operations and physiologic experiments on animals.

Symbolic decorations have largely replaced conventional decorations throughout the building. Above the doorway are grouped low bas reliefs of the heads of representative pathologists from various countries: Morgagni, Italy; John Hunter, England; Bichat, France; Virchow, Germany; Rokitansky, Austria; Welch, America; Cohnheim, experimental pathology; and Pasteur, bacteriology and immunology. Bronze doors are decorated with zodiacal signs of Libra and Cancer, medieval lancets, medieval urine glass, pine cone and the Tudor rose. A frieze over the door alternates the cock and the pine cone. The panel over the door shows the American form of the caduceus over which is an open book with the inscription from Claude Bernard, "Observation shows and experiment teaches." Six designs are repeated in the panels under the windows and are the motifs from escutcheons of the medieval guilds; namely, Barber Surgeons of London, Physicians of London, Barber Surgeons of Brussels, Barber Surgeons of Edinburgh, and Apothecaries of Nuremberg with the shield of the Medici of the Della Robbia period representing Italy. Interior grilles utilize much the same material as the bronze doors. A frieze around the main corridor utilizes the caduceus and the pine cone. The lamp shades in the library are decorated with the trademarks of eight of the great medieval and early renaissance printers and publishers. The interior of the building is of simple construction with the exception of decorative features in the library, chapel, entrance hall and director's office.

The dedicatory exercises will take place Oct. 7, 1929, and a general invitation is extended to all who may be interested. The exercises will be presided over by the president of the university, Dr. Robert Ernest Vinson. Brief addresses will be made by President Vinson, Torald Sollmann, dean of the medical school, and

Howard T. Karsner, director of the institute. The dedicatory address will be delivered by Henry Roy Dean, professor of pathology in the University of Cambridge. Honorary degrees will be conferred on Professor Dean, Dr. William H. Welch, William T. Councilman, Ludvig Hektoen and Simon Flexner. Preceding the dedicatory exercises, which will take place at 5 o'clock in the afternoon, the building will be open for inspection. Following the dedicatory exercises a dinner will be given by President Vinson to the delegates from institutions of higher rank and the learned societies.

**University News, Promotions, Resignations and Appointments.**—Dr. Timothy Leary has resigned as professor of pathology, bacteriology and medical jurisprudence at Tufts College Medical School, Boston, after about thirty-two years of service.

Dr. George S. Silliman, Abingdon, has accepted a position as roentgenologist and pathologist at the Methodist Hospital, Gary, Ind.

Dr. Allan W. Blair, formerly of the Pathological Institute of the Royal Victoria Hospital, McGill University, Montreal, has been appointed instructor in pathology and bacteriology at the University of Alabama School of Medicine.

Dr. Jean R. Oliver, professor of pathology, Stanford University Medical School, San Francisco, has been appointed professor of pathology at the Long Island College Hospital, Brooklyn, to succeed Dr. Archibald Murray, the appointment to become effective July 1. Before going to Stanford, Dr. Oliver was with the Rockefeller Institute, New York.

The dean of the University of California Medical School, San Francisco, announces the following appointments and promotions in the faculty, effective July 1: Dr. Isabel H. Perry, pathology; Dr. Adelbert M. Moody, pathology; Dr. Stacy R. Mettier, assistant professor of medicine and pathology; Dr. Zera E. Bolin from instructor to assistant professor of pathology; Dr. James F. Rinehart from assistant to instructor in pathology.

Prof. Oskar Frankl of Vienna will give twenty lectures on gynecologic physiology and pathology, and ten lectures on endocrinology at the Woman's Medical College of Pennsylvania, September 10 to 26.

The following appointments for the next academic year have been made by the medical fellowship board of the National Research Council, of which Dr. Gotthelf Carl Huber, professor of anatomy, University of Michigan School of Medicine, is chairman: Claude Forkner, pathology and clinical investigation; Emidio L. Gaspari, bacteriology and immunology; Leone McGregor, pathology, and Bruce Webster, internal medicine.

**Milwaukee Academy of Medicine.**—The Milwaukee Academy of Medicine was addressed on May 28, by Dr. Charles H. Bunting, professor of pathology, University of Wisconsin Medical School, on "Diseases of the Bone Marrow and Lymph Glands."

**American Psychopathological Association.**—Dr. James Ramsay Hunt, New York, was elected vice president, and L. E. Emerson, Cambridge, Mass., secretary, of the American Psychopathological Association at a meeting held in Atlanta, Ga., on May 17.

**Cancer Registry Established.**—Local physicians will establish city-wide cancer and abnormal growth registry, at the Research Institute of the Lankenau Hospital in September. All types of tumors will be preserved to assist the diagnosis and study of these growths. A feature of the registry will be a follow-up service in which nurses provided by the Philadelphia Health Council will visit patients after they have had cancerous or noncancerous growths removed to report to what extent surgical treatment has been beneficial. The registry is being organized by Dr. Stanley P. Reimann, director of the research institute of the hospital. Its head will be Dr. Joseph McFarland, professor of pathology, University of Pennsylvania School of Medicine.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

JUVENILE ACRODYNIA. C. W. WYCKOFF, Am. J. Dis. Child. **37**:88, 1929.

The author, by a process of elimination, arrives at the conclusion that a subacute infection is the cause of acrodynia. The symptoms are objective. Extreme restlessness, sleeplessness and irritability are manifest. The child never plays, and it lies down in a crouching position with the abdomen supported by the thighs. The cardinal symptom is redness and swelling of the extremities with desquamation. The remaining symptoms are anorexia and asthenia. The child becomes emaciated, a rash appears, teeth fall out and there is a diminution of sensitiveness to external stimuli. Byfield claims that the condition is one of peripheral neuritis involving mainly the sensory nerves and showing marked vasomotor disturbances of the extremities. The treatment advised consists of removal of the tonsils and adenoids. The use of hypnotics is not advisable. Calamine lotion is used for the eruption of the skin and itching. The main object in treatment is to maintain a fair state of nutrition.

H. E. LANDT.

HYPERTENSION IN THE YOUNG. SAMUEL AMBERG, Am. J. Dis. Child. **37**:335, 1929.

Different forms of hypertension, persisting for long periods, can occur in childhood. The cases reported here represent: (1) hypertension associated with coarctation of the aorta—in these cases the elevation in blood pressure is confined to the upper part of the body; (2) hypertension associated with cardiac decompensation; (3) hypertension intimately associated with disease of the kidney—in such cases it may be of shorter or longer duration and at times be referable to increased intracranial pressure; (4) hypertension as the consequence of an organic cerebral lesion; (5) hypertension perhaps in the form of so-called essential hypertension, and (6) hypertension in the form of a syndrome of malignant hypertension as described by Keith, Wagener and Kernohan, with changes mainly in the small arteries and arterioles.

AUTHOR'S SUMMARY.

MUSCULAR HYPOTONIA ASSOCIATED WITH CONGENITAL HEART DISEASE. C. DAVISON and MORRIS M. WEISS, Am. J. Dis. Child. **37**:359, 1929.

A case of congenital heart disease associated with a marked hypotonia is reported. If the hypotonia is an anomaly, as others occurring in a congenital cardiac condition, then this is the first case of its kind reported. If the hypotonia does not have a relationship to the cardiac condition, the only disease that it simulates is amyotonia congenita, in which case it would be an atypical form of this entity.

AUTHORS' SUMMARY.

THE PROGRESSIVE ANEMIA FOLLOWING A SINGLE INTRAMARROW INJECTION OF *B. WELCHII* TOXINS. JOHN C. TORREY and MORTON C. KAHN, Am. J. Path. **5**:117, 1929.

It has been found that the single inoculation of 0.5 cc. of a potent sterile *B. welchii* toxin into a tibial marrow of a rabbit or a monkey gives rise to a chronic, persistent and finally often fatal anemia, characterized by low hemoglobin content of the blood, low erythrocyte count and a color index generally above 1. Anisocytosis and at times poikilocytosis are pronounced. A single intravenous inoculation of *B. welchii* toxin of the same dosage, or a series of increasing doses, gives rise to an anemia of the same type as that resulting from inoculation of the marrow, but is followed within from three to four weeks by an immunity and a

return of the blood to a normal or nearly normal condition. Such intravenous inoculation of the toxin causes some mucous degeneration of the fat cells and an increase in the cellular elements in the marrow, particularly the leukocytes, but results in nothing like the destructive action of inoculation directly into the marrow. The single inoculation of 0.5 cc. of the toxin into a tibial marrow starts a degenerative process which apparently affects the whole marrow system. Definite evidence of beginning degenerative changes were noted in the marrows on the side of the body opposite the site of inoculation within eighteen hours. After twelve days the process was well advanced as shown by the marked mucous degeneration of the fat cells, great diminution in other normal marrow and blood-forming cells and a marked increase in polymorphonuclear leukocytes. In rabbits which had died eleven or more weeks after the inoculation the marrows were found to be in an advanced stage of degeneration, with fat cells replaced by a granular material and an extreme atrophy of the cellular elements. Nearly all the animals showed, at whatever stage examined, a rather more pronounced degeneration in marrows far removed than in that into which the toxin was injected. As intravenous inoculation of like or larger amounts of toxin causes no more than a transitory injury to the marrow, the cause of the difference in effect is not clear. It is suggested that the chronic experimental anemia produced in this way may prove a useful means for evaluating the potency of extracts of liver and other organs as blood regenerating agents.

AUTHORS' SUMMARY.

THE SYNDROME PRODUCED BY ANEURYSM AT OR NEAR THE JUNCTION OF THE INTERNAL CAROTID ARTERY AND THE CIRCLE OF WILLIS. FULLER ALBRIGHT, *Bull. Johns Hopkins Hosp.* **44**:215, 1929.

The symptoms in two patients, on whom the diagnosis of ruptured intracranial aneurysm near the junction of the internal carotid artery and the circle of Willis was made, are reported with the results of autopsy in one case. Thirty cases of aneurysm in this region in which there were localizing symptoms before death are abstracted from the literature. The entire series of thirty-two cases fall into five etiologic groups: mycotic, traumatic, syphilitic, arteriosclerotic and congenital. The symptomatology can be divided into two main subgroups, neighborhood symptoms due to involvement of structures in this region, and symptoms arising from leakage of blood into the subarachnoid space. The neighborhood symptoms, except in the larger aneurysms, as a rule become manifest only after partial rupture of the aneurysm and the formation of a false aneurysm. The commonest neighborhood symptoms are internal and external paralysis of the third nerve and involvement of the first branch of the fifth nerve. The third nerve was involved in every case in the series. Relief of pain by obliteration of the common carotid artery in the neck was a helpful diagnostic sign in one of my cases. The internal carotid artery was ligated in the neck without success in one of the newly reported cases. The possibility of relieving this condition by surgical measures is discussed, but no conclusions are reached.

AUTHOR'S SUMMARY.

OUTLYING ACIDOSIS DUE TO FUNCTIONAL ISCHEMIA. PEYTON ROUS and DOUGLAS R. DRURY, *J. Exper. Med.* **49**:435, 1929.

In various functional conditions involving peripheral vasoconstriction, a more or less widespread change toward acidity takes place within certain tissues. The change is frequently independent of any in the blood. Indeed, the blood can become more alkaline while the tissue acidosis is developing. When the blood volume is diminished abruptly but not too greatly, by hemorrhage or by anhydremia, the acidosis which develops in the superficial connective tissue and\*in the skeletal muscles is patchy in distribution, being limited to areas of local ischemia themselves the result of a compensatory vasoconstriction which affects certain regions only. There is a second type of patchy ischemia (and of acidosis) which occurs under circumstances of moderate depletion and is referable to local pressure differences

that are so slight as to be ineffective under normal circumstances. A generalized acidosis throughout the superficial tissue develops when depletion is extreme. All these are outlying acidoses, since they lie without the influence of the blood. In the viscera no such acidoses have been found.

AUTHORS' SUMMARY.

TREATMENT OF EXPERIMENTAL ACUTE GENERAL PERITONITIS IN THE DOG WITH ILEOSTOMY AND SODIUM CHLORIDE SOLUTION. THOMAS G. ORR and RUSSELL L. HADEN, *J. Exper. Med.* **49**:525, 1929.

In experimentally produced general peritonitis, drainage of the gut by ileostomy 6 inches (15.24 cm.) above the cecum has no beneficial effect. Animals with experimentally produced general peritonitis treated with ileostomy plus 1 per cent sodium chloride solution live three times as long as those not given the salt solution.

AUTHORS' SUMMARY.

THE RAPID SHALLOW BREATHING FROM PULMONARY CONGESTION AND EDEMA. EDWARD D. CHURCHILL and OLIVER COPE, *J. Exper. Med.* **49**:531, 1929.

These experiments record the effects of the experimental production of pulmonary congestion and edema in a lung completely isolated from the general circulation, but with an intact nerve supply. The resulting changes are: a slowing of the heart rate, a fall in systemic blood pressure and a temporary inhibition of respiration succeeded by rapid shallow breathing. The pulse rate and blood pressure show a rapid and spontaneous return to initial conditions. The respirations show a partial but not a complete return to their former rate and depth. The effects on respiration are similar to those described by Dunn and Binger and Moore which follow multiple embolism of the pulmonary circuit with starch granules. The alterations in the pulse rate and blood pressure are characteristic of the effects of vagal stimulation. A chemical effect on the respiratory center is excluded by the nature of the preparation. These results, therefore, add further evidence to support the hypothesis that the rapid shallow breathing present in congestion and edema of the lungs is due to the stimulation of nerve endings in the lungs.

AUTHORS' SUMMARY.

BLOOD CHLORIDES IN CONDITIONS ASSOCIATED WITH PNEUMONIA. CARL A. L. BINGER, RONALD V. CHRISTIE, JOHN STAIGE DAVIS, JR., and ALMA HILLER, *J. Exper. Med.* **49**:603, 1929.

Attempts have been made in dogs to lower the chlorides in the serum by means of various procedures. Of these the withholding of food, anoxemia, tissue destruction, anaphylactic shock, leukocytosis and fever yielded negative results. The ingestion of large amounts of water lowered the chloride level independently of body temperature. The drop in chlorides under these circumstances could not be accounted for by excretion and appeared to run parallel with an increase in the water content of the serum. Experimental pneumococcus infection in two animals reduced the chloride concentration in the serum.

AUTHORS' SUMMARY.

ARTERIAL CARBON DIOXIDE PRESSURE IN CARDIAC DYSPNEA. F. R. FRASER, C. F. HARRIS, R. H. HILTON and G. C. LINDER, *Quart. J. Med.* **22**:1, 1928.

Fifty cubic centimeters of blood was drawn from the femoral arteries of patients with cardiac dyspnea into paraffined syringes containing potassium oxalate and sodium fluoride. This was kept surrounded by ice. Four portions of 10 cc. each were successively transferred to tonometers of 400 cc. capacity, filled with mixtures of air and carbon dioxide so that the pressure of carbon dioxide was 20, 30, 40 and 50 mm. of mercury. The volume of carbon dioxide in the blood from the tonometer was plotted against the pressure of carbon dioxide in the tonometer, and a dissociation curve constructed. The point in the curve corresponding to the volume of



carbon dioxide in the arterial blood gave an estimation of the arterial carbon dioxide pressure. This was further checked by plotting the carbon dioxide pressure in the tonometer against the hydrogen ion concentration of the blood removed from the tonometer. The results of this study indicate that in the absence of such factors as pulmonary disease and the changes that occur in dying tissues cardiac dyspnea is characterized by a low carbon dioxide pressure in the arterial blood. As the degree of heart failure and the dyspnea diminish, the pressure of the carbon dioxide rises. The low carbon dioxide pressure is associated with an arterial hydrogen ion concentration which is on the alkaline half of the normal range. This is significant in that it indicates that an increased acidity of the blood supplied to the respiratory center is not the cause of the increased respiratory activity. The combination of the low carbon dioxide pressure and the low normal carbon dioxide capacity, and the values of the hydrogen ion on the alkaline side are indicative of a dyspnea due to the stimulation of the respiratory center, but which is independent of the character of the blood supplied to the center. Thus, this stimulus may be due to low oxygen tension in the tissues of the center, which would result from a lowered minute volume of the circulation. In those cases in which there is pulmonary disease in addition to heart failure, or those in which pulmonary lesions are seen in severe passive congestion, the arterial carbon dioxide pressure is raised. This is probably the result of inefficient pulmonary ventilation, and the raised carbon dioxide acts as an additional stimulus to the respiratory center. An additional factor is the increased hydrogen ion concentration which occurs shortly before death; this would act as an additional stimulus to the center.

N. ENZER.

GOUT. P. E. A. NYLANDER, Arb. a. d. Path. Inst. d. Universität. Helsingfors 5: 381, 1928.

It is probable that gout is related to vasomotor and trophic neuroses. That disturbances of calcium metabolism play a rôle in gout is not established; the calcareous deposits in gout are probably not the direct result of increase in the blood calcium.

THE GASEOUS METABOLISM IN TUBERCULOSIS WITH SPECIAL REFERENCE TO THE SPECIFIC-DYNAMIC ACTION OF PROTEINS. F. SALUS and H. ADLER, Beitr. z. Klin. d. Tuberk. 70:733, 1928.

The basal metabolism in afebrile, noncachectic tuberculous patients may be normal, increased or decreased. Basal metabolic determinations cannot be used for the diagnosis of activity. Tuberculous patients show frequently greater fluctuations in the basal metabolic rate than normal persons. Artificial pneumothorax has no influence on the basal metabolic rate. The specific-dynamic action of proteins was found decreased in 15 per cent, normal in from 15 to 30 per cent and increased in more than 30 per cent of the patients. These deviations do not show any correlation with the pulmonary process, but they are definitely dependent on the allergy of the patient. Increased protein action is frequently associated with alimentary hyperthermia. These studies suggest that a diet low in proteins may be indicated in certain tuberculous patients.

MAX PINNER.

CHANGES ACCOMPANYING WORK AND FATIGUE OF MUSCLE. L. WACKER, Klin. Wchenschr. 8:244, 1929.

The content of calcium and magnesium is increased considerably in the blood of rabbits fatigued by an alternating electrical current during urethane narcosis. The increase of the calcium in the serum averages 50 per cent, and of the magnesium about 140 per cent, that of the resting values in urethane narcosis. The increase in magnesium is relatively greater than that in calcium. The quotient  $\frac{\text{Ca.}}{\text{Mg.}}$  diminished from  $\frac{10.84}{2.93} = 4.16$  in the nonfatigued animal to  $\frac{18.03}{7.01} = 2.57$  in the fatigued animal. The increase of calcium and magnesium in the blood with

fatigue disappears after several hours of rest. The high calcium and magnesium content of the blood in fatigued animals is derived probably from the muscle, the bases being liberated from the earthy phosphates dissolved by the muscle acidity and then transferred to the blood. With magnesium narcosis the magnesium content of the serum exceeds the calcium and the  $\frac{\text{Ca.}}{\text{Mg.}}$  quotient  $\frac{9.40}{19.41}$  diminishes to 0.48. Part of the calcium is replaced by magnesium. In the normal rabbit serum the calcium is 11.84 mg. per hundred cubic centimeters; in the narcosed animal 9.40 mg. per hundred cubic centimeters.

AUTHOR'S SUMMARY.

OVARIAN HORMONE AND METABOLISM. GERTRUD KOEHLER, *Klin. Wchnschr.* 8:502, 1929.

The metabolic rate in eight women and two men was not altered by the administration of ovarian hormone.

EDWIN F. HIRSCH.

CARBOHYDRATE METABOLISM AND THE OXIDATION OF THE GLUCOSE MOLECULE. E. SCHNEIDER and E. WIDMANN, *Klin. Wchnschr.* 8:536, 1929.

Lactic acid injected intravenously is synthesized to glycogen. Dioxyaceton is completely oxidized. Methylglyoxal, on the contrary, to some extent is synthesized to glycogen through lactic acid.

AUTHORS' SUMMARY.

### Pathologic Anatomy

HEART-BLOCK SHOWING MULTIPLE TRANSITIONS ASSOCIATED WITH CONVULSIVE SYNCOPÉ. WALLACE M. YATER and FREDERICK A. WILLIUS, *Am. Heart J.* 4:280, 1929.

A case is reported with detailed pathologic data. Also, the literature on the pathology of heart block is reviewed briefly and a bibliography is furnished. Directions are given for taking sections at the autopsy table to aid in locating the lesions in heart block.

PEARL ZEEK.

HEMANGIOBLASTOMA OF THE CEREBELLUM (LINDAU'S DISEASE). LEO M. DAVIDOFF, *Am. J. Path.* 5:141, 1929.

The practical importance of a knowledge of these tumors is, in the first place, that when they occur alone they are completely removable surgically with a resulting cure of the condition. Secondly, in the presence of all tumors of the cerebellar hemispheres, one must, knowing the associated lesions in cases of Lindau's disease, be on the lookout for angiomas of retinae and tumors of the medulla, spinal cord, pancreas, kidneys, suprarenal glands, epididymi, etc., especially if material gained by operation proves histologically to be hemangiomas in character. The prognosis in the complicated cases should be guarded even if the cerebellar tumor is removed in its entirety.

AUTHOR'S SUMMARY.

THE EFFECT OF COMBINED FEEDING OF POTASSIUM IODIDE AND ANTERIOR LOBE OF THE PITUITARY UPON THE THYROID GLAND. HOWARD ANDERSON MCCORDOCK, *Am. J. Path.* 5:171, 1929.

Oral administration of anterior pituitary tablets causes a depression in the activity of the thyroid gland with a marked lowering of the number of mitoses in the entire gland and with medium-sized or somewhat smaller acini distended with hard colloid compressing the lining epithelium into thin strands of cells. During the first stage of its action, potassium iodide, on the other hand, produces marked stimulation with enormous mitotic activity and a slightly softened colloid occasionally containing large numbers of phagocytic cells. The early proliferative change induced in the thyroid gland by potassium iodide is prevented by anterior pituitary when both these substances are fed to the same animal.

AUTHOR'S SUMMARY.

FENESTRATIONS OF THE SEMILUNAR VALVES. ARTHUR N. FOXE, *Am. J. Path.* 5:179, 1929.

In a series of 300 cases, one or more fenestrations occurred with a frequency of 82 per cent. The frequency of pulmonic and aortic involvement was approximately equal. Fenestrations, which are acquired defects, increase in frequency with age. Patent foramen ovale, which is a developmental defect, decreases in frequency with age. The total percentage for the frequency of the occurrence of this defect was 22. The classification, nature and variety of the fenestrations are briefly discussed. It is possible that fenestrations may occasionally cause an aortic insufficiency.

AUTHOR'S SUMMARY.

INTRA-MEDULLARY LIPOMA OF THE SPINAL CORD. E. SACHS and E. F. FINCHER, *Arch. Surg.* 17:829, 1928.

A lipoma beneath the dura, at the level of the sixth thoracic vertebra, was found to be imbedded in the cord. Sections showed it to be composed entirely of fatty tissue. The condition is rare. One writer previously collected nine cases, some of which the authors feel are not pure lipomas. Of fourteen intramedullary tumors reported by Elsberg, not one was lipomatous.

N. ENZER.

HEMANGIOMA OF THE KIDNEY. H. H. CRILE, *Surg. Gynec. Obst.* 48:449, 1929.

A 6 by 6 cm. cystic and fluctuating cavernous hemangioma, located on the anterior aspect of the anteroexternal surface of the kidney, produced sudden severe pain in the right lower abdominal quadrant and the passage of blood clots in the urine in a white man, aged 37. No communication was found between the tumor and the pelvis of the kidney although the remaining portion of the renal calices contained blood. The microscopic picture was that of a typical cavernous hemangioma.

RICHARD A. LIFVENDAHL.

ABERRANT BLOOD VESSELS AS A FACTOR IN LOWER URETERAL OBSTRUCTION. JOSEPH A. HYAMS, *Surg. Gynec. Obst.* 48:474, 1929.

An aberrant artery running in a band of fibrous tissue caused constriction of the right ureter, from 6 to 8 cm. above the ureteral orifice. Proximal to this constriction there was a calculus, above which the ureter was dilated. The patient suffered sharp intermittent pains over the sacro-iliac region and the kidneys at intervals of five or six months for a period of three years. From dissection of cadavers the author found that there was considerable variation in the course and distribution of the vessels of the pelvis in the vicinity of the ureters. In one body he noted a similar constricting band of the ureter as in the aforementioned patient.

RICHARD A. LIFVENDAHL.

CONGENITAL VALVULAR OBSTRUCTION OF THE PROSTATIC URETHRA. H. H. YOUNG and R. W. MCKAY, *Surg. Gynec. Obst.* 48:509, 1929.

The authors report fifty-one cases of congenital valvular obstruction of the urethra in persons from 11 days to 57 years of age. The condition is described as an obstructing fold of mucous membrane coming from the vesicle neck in the form of semilunar valves, as a diaphragmatic membrane below the verumontanum, or as a fold running downward from the prostatic orifice anteriorly. As a result of this obstruction to the outflow of urine there is a funnel-shaped dilatation of the prostatic urethra and vesicle neck. If the obstruction is marked or if the condition is of long duration, the urinary bladder, ureteral orifices, ureters and the renal pelves may be markedly dilated. The authors divide the condition into three types depending on the position and character of the obstructing valves. The importance of early cystoscopic examination, the prognosis and the treatment are discussed.

RICHARD A. LIFVENDAHL.

THE BLOOD SUPPLY OF THE THYROID GLAND WITH SPECIAL REFERENCE TO THE VASCULAR SYSTEM OF THE CRETIN GOITRE. O. H. WANGENSTEIN, Surg. Gynec. Obst. 48:613, 1929.

The blood supply of thirty-nine thyroid glands was studied after intra-arterial injection, with the glands submerged in normal physiologic solution of sodium chloride, some following the instillation of diluted ink, in a few cases, roentgen examinations followed the injection of mercuric oxide and Hill's white paste. The inferior thyroid artery was found to be considerably larger than the superior, and in several of the cretin goiters the former had a diameter of 9 mm. In the seventeen specimens from necropsy the inferior thyroid was absent but the superior was always found; in two the vessel was small. One gland had a double superior thyroid artery. An accessory thyroid artery was observed twice in dissected postmortem specimens. An anomalous artery, in one cretin patient, which arose as a branch from the main division of the right superior thyroid artery ran obliquely across the isthmus and communicated with the left inferior thyroid artery. The free anastomosis between the subcapsular vessels was well demonstrated in the various methods of injection. There seemed to be no direct relation between the size of the goiter and its arteries. A few injections of the veins revealed great friability of their walls with rupture and dissemination of the injected material into the adjacent tissue.

In cretin goiters intimal thickening was frequently observed, and in many instances almost complete occlusion of the lumen was noted in the arteries of the capsule and in those of the second order; even the follicular and interlobar branches were the site of degenerative changes. The muscular walls of the larger groups of vessels were often very thin. The interfollicular network of colloid goiters was narrowed and compressed, and their capillary communications were often absent. The adenomatous glands revealed changes similar to those of the cretin goiters; in both, areas of hyperplasia were surrounded by capillaries which appeared more like the normal vessels. This marked enlargement of the extra-glandular vessels is regarded as a compensatory effort to bring as good blood supply as possible to the adenomatous areas of physiologically hypo-active tissue, as alterations in the stroma have made a normal nutrition impossible.

RICHARD A. LIFVENDAHL.

ADENOMA OF THE KIDNEY. H. L. KRETSCHMER and C. DOEHRING, Surg. Gynec. Obst. 48:629, 1929.

A thick bluish-white membrane, from 0.5 to 1 mm., encapsulated a tumor, 12 by 15 by 15.5 cm., weighing 760 Gm. that arose from the right kidney, leaving a small residual portion of the kidney which was located on the upper pole of the tumor. This mass, which was of uniform consistency, was composed of cuboidal or hexagonal cells in more or less alveolar arrangement. The nuclei of the cells were large and contained an abundant chromatin content. In the literature sixteen similar cases were found, the youngest in a girl, 11 months of age. The genesis is ascribed to rests of renal tubules, error in development, remnants of the Wolffian body, or the possibility the tumor cells may be the offspring of cells which were destined to form kidney substance but were early diverted to the formation of a tumor. There has been no recurrence four years after the removal the adenoma in the case described.

RICHARD A. LIFVENDAHL.

TORTICOLLIS; REMOVAL IN EARLY LIFE OF THE FIBROUS MASS FROM THE STERNOMASTOID MUSCLE. H. LEROY VON LACKUM, Surg. Gynec. Obst. 48:691, 1929.

Four infants with congenital torticollis with localized swellings in the sternomastoid muscles obtained marked relief after the removal of thick scar tissue from the muscle. Microscopically, this tissue consisted of connective and dense scar tissue in which muscle fibers occurred singly and in groups.

RICHARD A. LIFVENDAHL.

SQUAMOUS CELL CARCINOMA IN A DERMOID CYST OF THE OVARY. J. C. MASSON and N. C. OCHSENHIRT, Surg. Gynec. & Obst. **48**:702, 1929.

Three cases of squamous cell carcinoma in dermoid cysts are added to thirty-three which were previously reported. The importance of careful microscopic examination of every dermoid cyst of the ovary is emphasized.

RICHARD A. LIFVENDAHL.

CONGENITAL ECTODERMAL DEFECT. H. MACKAY and A. M. DAVIDSON, Brit. J. Dermat. **41**:1, 1929.

Eleven instances of hypotrichosis, dental aplasia, and disturbance in taste and smell are reported in five generations of the same family. The facial expression is characteristic and the glands of the skin are absent or rudimentary.

A RARE VOLUMINOUS LEIOMYOMA OF THE LUNGS. ENRICO EMILIO FRANCO, Tumori **3**:27, 1929.

At the autopsy of a woman, aged 56 years, Franco found in the upper lobe of the right lung an ovoid tumor mass measuring 13 by 11 cm.; attached to its side there was a second mass, about one-half the size of a hen's egg. On microscopic examination the tumor proved to be a fibro-myoma. No primary growth was discovered elsewhere in the body.

W. OPHÜLS.

MORPHOLOGY AND PHYSIOLOGY OF THE NORTH AMERICAN GOITER. C. ALEXANDER HELLWIG, Arch. f. klin. Chir. **154**:1, 1929.

Of 160 goiters obtained by operation at the Halstead Hospital, Halstead, Kan., 53 per cent were diffuse and 47 per cent nodular. Congenital goiters were not observed. The diffuse hyperplasias in puberty and pregnancy were macrofollicular colloid goiters. Microscopic examination revealed the surprising fact that two thirds of the so-called primary exophthalmic goiters were developed from the diffuse colloid goiters. Only 4 per cent of the thyrotoxic patients had parenchymatous (fetal) adenomas. Seventy-five per cent of the nodular goiters were composed of small multiple colloid nodules. The majority of those goiters caused thyrotoxic symptoms, usually not before the age of 40 years.

AUTHOR'S SUMMARY.

PLEURAL EFFUSIONS: THEIR MORPHOLOGY. A. ARNSTEIN and M. HUPPERT, Beitr. z. Klin. d. Tuberk. **70**:660, 1928.

The cytologic observations in 115 pleural effusions are reported. It is pointed out that effusions of various etiology (hydrothorax, tumors and inflammatory exudates) cannot safely be differentiated by morphologic examinations. Certain characteristics, such as hemorrhagic appearance and lymphocytosis, may be helpful in arriving at a diagnosis.

MAX PINNER.

HISTOLOGIC EXAMINATION OF CAVITIES AND BRONCHIECTASIS: THE HEALING OF CAVITIES. E. MELZER, Beitr. z. Klinik. d. Tuberk. **70**:694, 1928.

Complete anatomic healing of a cavity was not found in any of the examined patients. The histologic differentiation between healed cavities and bronchiectasis is possible in most of the cases. Bronchiectasis must be diagnosed if any one of the following structures are found in the wall: high cylindrical epithelium, circular or longitudinal smooth musculature, circular elastic fibers, or cartilage. When cavities shrink, bronchiectasis with small inflammatory changes may develop in the neighborhood; these are caused by the mechanical tension of the tissue.

MAX PINNER.

ENDEMIC GOITER IN THE HOG. EDUARD CLERC, *Zieglers Beitr. z. path. Anat. u. z. allg. Path. Kinderh.* **76**:444, 1928.

Thyroid glands of the hog, obtained in the goiter belt of Bern (Switzerland) were compared with those from the northern coast of Germany. As early as in the first year of life the Swiss hogs show a distinct diffuse enlargement of the thyroid gland. Its histologic structure coincides entirely with that of human goiter and that of other animals. The first change in goiter formation is epithelial hyperplasia which either persists or, after some time, is converted into colloid goiter. The iodine content of the glands of Swiss hogs was much less than that in the German hogs. The incidence of goiter does not differ only in the same village, but also in animals of the same pen. Lack of iodine, therefore, cannot be regarded as the only factor in producing goiter; neither can the quantity and quality of the food and water play an important rôle. The hyperplastic goiter in pigs is accompanied, as a rule, by a low body weight.

C. A. HELLWIG.

VITAL STAINING REACTIONS OF THE LUNG. G. SEEMANN, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:1, 1927.

In continuation of previous work. Seemann studied the reaction of the lung to finely dispersed colloid (trypan blue), coarsely dispersed colloid (saccharated ferric oxide), and fine and coarse particulate matter in suspension (red mercuric sulphide and staphylococci). In most of the experiments, the mouse was used, and in a few, rats and rabbits. The material was introduced chiefly intravenously; in some experiments the intrapleural and intratracheal routes were employed. Wide difference of opinion still exists as to the relative activity of the capillary endothelium, the histiocytic elements and the alveolar epithelium of the lung in the matter of vital storage. Seemann found the lung taking up much less of the injected material than the liver or spleen. The capillary endothelium stored none of the injected materials. The alveolar epithelium was also inactive after intravenous injection, except in the cases of trypan blue. This caused a finely granular stippling of the nucleated alveolar lining cells, in contrast to the histiocytes in which the material was coarsely granular. Except for the small amount of trypan blue held by the alveolar epithelia, all of the stored material was in histiocytes and leukocytes. It was impossible to remove all the cells from within the vessels of the lung by perfusion, but the author believes that the storing histiocytes which he observed came from the blood stream and that the lung contains few or no elements belonging to the reticulo-endothelial system. Introduced intratracheally, cellular elements which the author holds to be alveolar epithelial actively phagocytized particulate matter; he concluded that the dust cells of the lung are epithelial in origin. Seemann reports the results of the parenteral introduction of foreign protein (casein and egg white) in solution. A single injection caused no demonstrable changes in the lung, contrary to the previously reported observations of Eller and of Siegmund, who had described vascular proliferative changes which often made their appearance from thirty to sixty minutes after the injection. Repeated injections also caused no changes in the lungs, but led to active hemopoiesis in the lymphoid tissues and in the spleen pulp. Protracted anaphylactic shock did not cause the swelling of the pulmonary capillary endothelium which was described previously by Domagk.

O. T. SCHULTZ.

AMNIOTIC ADHESIONS. J. OLOW, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:27, 1927.

On the basis of two cases studied in detail, Olow concludes that amniotic adhesions result from incomplete dehiscence of the ectodermal epithelium of the embryoblast in the formation of the amniotic cavity. A multilocular instead of a unilocular cavity is thus formed. During further development the septums are transformed into strandlike and membranous adhesions.

O. T. SCHULTZ.

DISTRIBUTION OF LIPOIDS AND GLYCOGEN IN NORMAL TISSUES. H. ARNDT, Beitr. z. path. Anat. u. z. allg. Path. **79**:69, 1927.

Arndt sought to gain insight into the cellular metabolism of fat and carbohydrate by microchemical study of the morphologic distribution of these substances in the tissues of a number of species of domestic animals. Of methods for demonstrating carbohydrates, only those for glycogen were found useful. The hope of detecting an interrelationship between lipid and carbohydrate materials within the cell was defeated by the fact that the methods for detecting the two groups of substances could not be applied to the same section. Both lipid substances and glycogen could often be seen in the same cell, but there was no way of determining an intracellular transformation of one into the other. The relative distribution of fat and glycogen in the lobule of the liver, the former being in the central zone and the glycogen being at the periphery, may permit the theoretical deduction that fat is transformed into glycogen where intracellular metabolism is more active. Glycogen was never found within the nuclei of the freshly fixed tissues of lower animals; this suggests that its fairly frequent intranuclear occurrence in human tissues is the result of a pathologic process.

O. T. SCHULTZ.

ISLANDS OF CARTILAGE IN VERTEBRAL BODIES. W. PUTSCHAR, Beitr. z. path. Anat. u. z. allg. Path. **79**:150, 1927.

In a woman who died of mammary carcinoma with metastases in the cervical vertebrae, islands of cartilage were found in the bodies of the affected vertebrae. To determine whether the presence of the cartilage bore any relation to the carcinoma or was only a chance association, the vertebrae were examined in seventy-two bodies of persons ranging in age from 10 days to 85 years. As a rule, the examination was limited to the two lower thoracic and the two first lumbar vertebrae. Cartilage was found in fifty-four cases, the youngest being 15 years old. In ten children under 15 years of age, no cartilage was found, indicating that the presence of cartilage in the vertebral bodies was not the result of embryonic maldevelopment. When present it occurred in the form of islands, usually about a millimeter in diameter, embedded within the bone. The islands were often multiple, sometimes coalesced with each other, and occasionally reached a diameter of from 5 to 10 mm. Sometimes the cartilage occurred as downgrowths directly continuous with the cartilaginous plate covering the vertebral body. The author believes that the misplaced cartilage results from resorption of bone about blood vessels which enter the bone, and subsequent mechanical displacement of cartilage from the surface plate into the defect thus produced. The misplaced cells then grow into the marrow spaces of the bone. When present in sufficient amount the cartilage may cause structural weakness of the bone.

O. T. SCHULTZ.

PATHOLOGY OF SUPRARENAL GLANDS IN RELATION TO ADDISON'S DISEASE. W. KOVÁCS, Beitr. z. path. Anat. u. z. allg. Path. **79**:213, 1928.

In the frequent tuberculous involvement of the suprarenal glands in Addison's disease, the destruction is usually so great that it is impossible to reach a conclusion as to the relative importance of medulla and of cortex in the syndrome. As a contribution to the solution of this problem and to the pathology of the suprarenal glands, Kovács presents a careful study of several interesting cases, together with the deductions which he thinks may be drawn from them. In a woman, aged 48 years, who had had the typical pigmentation of Addison's disease for many years but whose blood pressure was normal, the suprarenal glands were greatly reduced in size and consisted only of medulla. The cortex was almost entirely absent; it consisted only of the degenerated remnants of a few regenerated islands. Kovács ascribes the disappearance of the cortex to a toxic material which acted specifically on the cortical cells. He excludes a toxic infectious process by the absence of scar formation, and postulates the action of a toxic material derived from abnormal metabolism. The resulting cytotoxic atrophy of the cortex he

likens to the contracted kidney observed in gout. Because of the similarity he prefers the name contracted suprarenal gland to atrophy. The toxic destruction of cortical cells continued over a long period of time and was associated with localized, nodular regeneration of cortical tissue, which served to maintain life until the final degeneration of the regenerated islands. This case is one of Addison's disease with suprarenal involvement limited to the cortex. In a second patient, a woman, aged 36, thrombosis of the femoral vein became evident on the ninth day after delivery, which took place five months before death. At the beginning of the fourth month before death, pigmentation of the skin was evident; the further course was that of a rapidly progressing Addison's disease. Both the cortex and medulla of each suprarenal gland were greatly reduced in amount and infiltrated by lymphocytes. The cortex contained dense bands of fibrous tissue and areas of necrotic detritus with cholesterol crystals. The veins of the suprarenal gland were transformed into solid cords as the result of the organization of the thrombus which had occluded each. To this case of vascular contracted suprarenal gland, with involvement of both medulla and cortex of each suprarenal gland and with symptoms of Addison's disease during life, the author adds two cases of unilateral thrombosis of the suprarenal vein with hemorrhagic infarction and rapidly ensuing death, for the purpose of illustrating the primary involvement of the medulla in this process and the degree to which the cortex may be destroyed. Next is presented a case of unusual interest in a woman aged 26 who was known to have had lymphogranulomatosis for three years prior to death. This clinical diagnosis was substantiated at necropsy. There was no active tuberculosis, but the medulla of each suprarenal gland was transformed into a calcified mass, over which there was a cortex of normal thickness and appearance. No accessory suprarenal tissue could be found. Symptoms of Addison's disease had been absent during life, and no pigmentation was noted at necropsy. The calcification of the medulla is interpreted as a healed tuberculous process. There follow two cases of generalized tuberculosis, without symptoms of Addison's disease during life; each patient had advanced tuberculous involvement of both suprarenal glands but unchanged aberrant suprarenal tissue.

In this interesting array of material, Kovács sees proof that complete destruction of the suprarenal medulla does not lead to death, that complete or almost complete destruction of the cortex is incompatible with life, that the sudden destruction of the cortex leads to death within a short time, that the more gradual destruction is associated with the syndrome of Addison's disease, and that aberrant cortical tissue, if present in sufficient amount, can protect the body against the ill effects of loss of the suprarenal cortex. He does not take the extreme view that loss of cortical function alone is responsible for the complete syndrome of Addison's disease. Loss of medulla alone would cause no symptoms warranting a diagnosis of Addison's disease. Loss of cortex alone would lead to this diagnosis because of the characteristic pigmentation, but the characteristic low blood pressure would be absent, as in his case of cytotoxic cortical atrophy. He further concludes that each kind of tissue, cortical and medullary, can function alone and need not necessarily have an interrelationship with the other. Objective observations, interpretations and deductions are well presented.

O. T. SCHULTZ.

AUTOTRANSPLANTATION OF BONE. R. DE JOSSELIN DE JONG and P. H. EYKMAN VAN DER KEMP, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:268, 1928.

The authors are convinced that both surgical and experimental evidence indicates that autotransplantation of bone is uniformly much more successful than transplantation into another animal of the same species. Therefore, to study the fate of transplanted bone and the source of the newly formed bone they chose autotransplantation, using the rabbit as experimental animal. Bone with both periosteum and endosteum, bone with periosteum or endosteum alone and bone with neither periosteum nor endosteum was transplanted into the lumbar muscles of rabbits, and the material was examined at varying intervals after transplantation. Reimplantation of bone into the tibia and ulna was also tried. The bone corpuscles



of the transplanted bone degenerated, died and underwent lysis rapidly and completely. Substitution or rehabilitation of the old bone did not occur, after either transplantation or reimplantation. The authors are emphatic in the statement that the living bone ultimately present has resulted only from the active proliferation of the osteogenic tissue of the periosteum, or endosteum. If proliferation of osteogenic tissue and regeneration of bone are to occur, infection, hemorrhage, and unnecessary mechanical insult must be avoided, and conditions must be such that a new vascular supply for the transplanted bone can be quickly provided. During the most active stage of proliferation of the osteogenic tissue, the newly formed tissue is osteoid. This is resorbed and replaced by normal bone as the proliferative activity recedes. Under the conditions of the experiments the proliferating tissues of the site of transplantation did not take part in the formation of new bone.

O. T. SCHULTZ.

CHANGES IN SYMPATHETIC GANGLIONS IN RELATION TO EXPERIMENTAL CHOLESTEROL ARTERIOSCLEROSIS OF THE RABBIT. F. DANISCH, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:333, 1928.

Whether the arteriosclerosis of the aorta which occurs in rabbits that are fed a diet high in cholesterol is a process of degeneration or imbibition or is due in part also to mechanical factors has not been conclusively settled. The experiments of Danisch were designed to study the effects of changes in blood pressure on the production of cholesterol arteriosclerosis in the rabbit. Especial attention was paid to a microscopic study of the celiac ganglion, to determine whether changes here might help to cause arteriosclerosis through changes in blood pressure. Extirpation of the ganglion in normal rabbits caused wider fluctuations in blood pressure than normal, with a generally lower level. Intravenous injection of nicotine or epinephrine caused an earlier appearance of arteriosclerosis in animals that were given a diet high in cholesterol than in control animals. The ganglion cells of the celiac ganglion of animals fed cholesterol became degenerated and vacuolated. In more prolonged experiments some of the ganglion cells disappeared and were replaced by proliferated satellite cells. The changes noted are held to be purely degenerative and not inflammatory in character. Such changes are believed by the author to play a part in the development of the arteriosclerosis. In Danisch's experiments, 0.5 Gm. of cholesterol in linseed oil was fed daily by stomach tube. The highest levels of cholesterol in the blood varied in different animals and were usually reached after from ten to twelve weeks. Arteriosclerosis of the aorta began to appear when the level of blood cholesterol was between two and three times the normal amount. The article ends with eight pages of references to the literature.

O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF GASTRIC MUCOSA. F. BÜCHNER and H. MORITZ, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:400, 1928.

Büchner and Moritz made a detailed histologic study of the fundic portion of the stomach, paying especial attention to changes in the gastric channels (Magenstrasse). In three cases, heterotopia of the gastric mucosa to mucosa like that of the small intestine was noted; the change was limited, however, to the channels, the intervening mucosa being free. In two cases, a chronic ulcer was present at the pylorus, and in the third the scar of an ulcer was present at the same point. In one stomach heterotopic changes were present through the entire extent of the fundic mucosa, the histologic picture being that described by some writers in achylia gastrica. Eight stomachs showed no heterotopic changes; two of these were the seat of chronic pyloric ulcer. The limitation of the changes noted to the Magenstrasse in three of four stomachs which showed alteration of the heterotopic type lends support to the view that the mechanical irritation of food is a factor in the production of the changes, and may help explain the occurrence of gastric carcinoma at levels higher than is the rule for ulcer.

O. T. SCHULTZ.

ENDOCARDIAL POCKETS OF THE VENTRICULAR SEPTUM OF THE HEART. H. KAEWEL, Beitr. z. path. Anat. u. z. allg. Path. 79:431, 1928.

Ribbert disagreed with the view of Schminke and others that the endocardial ridges and pockets sometimes seen on the ventricular septum of the heart are the result solely of mechanical action. The ridges and pockets occur most often in the left ventricle, usually on the upper part of the septum. They are crescentic or horseshoe-shaped, with the concavity directed upward. More rarely they occur on the under surface of the aortic segment of the mitral valve, and occasionally they are found on the septum near the apex of the left ventricle; in this case, the concavity is directed downward. The author made a histologic study of twenty-five hearts in which septal ridges and pockets were noted. In fifteen hearts, the aortic valve was insufficient, eight times as the result of syphilis of the aorta and in the remainder as the result of chronic aortic endocarditis. In the syphilitic patients, the inflammatory process had led to the formation of narrow channels between the bases of the aortic segments. The pockets occurred directly in the course of the blood stream which flowed backward through these channels. In the nonsyphilitic patients with aortic regurgitation, the backflow of blood was also held responsible. In ten cases, chronic mitral endocarditis was present. In two of these, the pockets were formed where fibrotic vegetations had rubbed against the septum. In the remaining eight cases, relative aortic insufficiency was held responsible. The author believes that in all the hearts studied by him mechanical factors alone are sufficient to explain the formation of the pockets. In none could he find any evidence that the process which led to the formation of the pockets was initiated as a true inflammation in the form of localized mural endocarditis, as postulated by Ribbert. As the result of the mechanical action of the backflow of blood, the endocardium undergoes localized thickening in the form of bands where the mechanical insult is greatest. Continuous action of the backward flowing blood stream transforms the ridge into a pocket. When the latter is situated near the apex and opens downward, the condition results also mechanically from the action of the regurgitating blood stream, which is directed upward at the apex in a parabolic curve and impinges against the lower portion of the septum.

O. T. SCHULTZ.

ACQUIRED BRONCHIECTASIS. H. SCHNEIDER, Beitr. z. path. Anat. u. z. allg. Path. 79:466, 1928.

Schneider divides acquired bronchiectasis into an atrophic form, which is usually cylindric, and a hypertrophic form, which is usually saccular. Both types occur most frequently in the lower lobes of the lung and are often bilateral; involvement of an upper lobe alone is rare. In the atrophic form the bronchial wall is thinned in larger areas and dilatation results from intrabronchial air pressure. Secondary inflammation may lead to thickening of the wall. Without inflammation the wall may become sclerotic. In the hypertrophic form, the bronchial wall becomes thickened as the result of interstitial inflammation, which disrupts the muscle fibers. The inflammatory process usually occurs in localized areas, so that the dilatation is saccular. With more widespread involvement of the wall, this type may also become cylindric. In this type intrabronchial air pressure is also the main factor, although traction exerted by peribronchial fibrosis may play a part. The hypertrophic saccular form most often follows pneumonia. Traction by an adherent pleura is of little importance in the causation of bronchiectasis.

O. T. SCHULTZ.

LIPOID NEPHROSIS. K. LÖWENTHAL, Beitr. z. path. Anat. u. z. allg. Path. 79:497, 1928.

The author claims that lipid nephrosis has received inadequate attention in the German literature. He now adds three cases to the two that he previously reported and brings the literature, especially the American, down to the date of appearance of his communication. He reiterates his former conclusion that so-called

lipoid nephrosis is primarily a disease of lipoid metabolism and that the part of the kidney in the process is merely that of an excretory organ. Protein metabolism is also abnormal. Because of the purely secondary rôle of the kidney in the process, he deprecates the use of the name lipoid nephrosis, and proposes protein lipoid diabetes as a preferable term.

O. T. SCHULTZ.

ORIGIN OF DUST CELLS IN THE SPUTUM. A. ROSIN, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:625, 1928.

Since Arnold first described the phagocytic dust cells of the sputum in 1885, there has been lively controversy over the origin of these cells. Origin from alveolar epithelium, from septal capillary endothelium and from inwandering histiocytes has been claimed by various groups of investigators. Arnold himself described two types of dust cell, the larger one derived from alveolar epithelium and the smaller from lymphocytes. Rosin vitally stained guinea-pigs with pyrrhol blue and subjected them to mechanical, chemical and bacterial irritation of the lung. Mechanical irritation was produced by rarefied atmosphere, chemical by the fumes of nitric acid, and bacterial by setting up tuberculosis in the lungs. His results were negative after intravenous injection of the dye, no vitally stained cells appearing in the bronchial secretion. When the dye was introduced intratracheally, large vitally stained cells appeared in the bronchial secretion and could be seen in microscopic sections of the lungs. If the dye was in suspension, granules could be seen within the still attached and flattened alveolar epithelia within two minutes. If the stain was in solution the same cells were diffusely stained within twenty minutes; after a slightly longer period the dye within the cells was granular. The author concludes that the phagocytic cells of the sputum are alveolar epithelia.

O. T. SCHULTZ.

GIANT CRYSTALLOID CASTS IN THE KIDNEYS IN A CASE OF MULTIPLE MYELOMA. H. O. KLEINE, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:678, 1928.

In a case of multiple myeloma, Kleine noted the occurrence of huge casts of peculiar composition in the dilated tubules of the kidneys. The casts consisted of an outer granular matrix which contained blood pigment and a doubly refractile crystalloid center. The urine contained Bence-Jones protein, but no mention is made of the presence of casts in the urine like those seen in the kidney. The presence of giant cells and leukocytes about the casts proves that the casts were not formed post mortem. Löhlein had described similar casts in the kidney in 1921, this being the only other report of such an operation, according to the author. The myeloma was of the plasma cell type. The mucosa of the stomach and small intestine was thin and atrophic. Amyloidosis was present in the internal organs. On the basis of the atrophic gastro-enteritis present in his case, the author builds a new theory of the pathogenesis of multiple myeloma. He supposes that incompletely digested protein is absorbed from the intestine, acts like parenterally introduced protein, and leads to amyloidosis. As a protective mechanism it also stimulates one or the other type of cell of the hematopoietic system to proliferation. By the action of cellular agglutinins formed locally, the newly formed hematopoietic cells are agglutinated and do not enter the circulation, thus forming the myeloma nodules.

O. T. SCHULTZ.

PATHOGENESIS OF TOLYLENEDIAMINE ICTERUS. H. EITEL, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:700, 1928.

Earlier work on the icterus which follows the subcutaneous injection of tolylenediamine into dogs led to the conclusion that this is a purely hemolytic form of jaundice, due to the destruction of erythrocytes within the circulation by the poison. Rosenthal, Melchior and Licht claimed that extirpation of the liver prevented the development of icterus after tolylenediamine or caused its disappearance if already present; they concluded that the jaundice was wholly

hepatogenous in origin. They ascribed the icterus to early damage to liver cells, which thus became incapable of forming bile, and interpreted their experiments as strong support of the older doctrine of Minkowski and Naunyn that there can be no jaundice without a liver to elaborate bile. Kodama claimed that biliary thrombi are already present in the liver after seven hours of tolylenediamine intoxication, thus introducing resorption of bile as the chief factor in the causation of the icterus. Eitel's problem was to determine the relative importance of retention due to damage to the liver cells and of resorption due to hindrance of outflow in the mechanism of tolylenediamine icterus. His work was limited to intoxications of thirty hours' duration and longer. At thirty hours the blood serum gave a direct van den Bergh reaction and the urine contained both bile acids and bile pigment, indicating a resorption icterus rather than a hemolytic one. The liver contained many bile thrombi in the smaller interlobular ducts. Such damage to the liver cells as was present was interpreted as the result of bile stasis rather than of a direct action of the poison on the liver cells. Whether the primary factor was damage to bile duct epithelium or increase in the viscosity of the bile he could not determine. The icterus is of the resorption type and is due to hindrance of outflow through the presence of biliary thrombi.

O. T. SCHULTZ.

EARLY STAGES OF TOLYLENEDIAMINE ICTERUS. D. YUASA, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:713, 1928.

Rosenthal, Melchior and Licht claimed that removal of the liver of dogs prevented the development of tolylenediamine icterus or caused its disappearance if already present. Kálláo asserted that the failure of bile formation in such experiments was due to the action of the dextrose necessary to maintain life in hepatectomized animals, and that bile pigment appears in the blood after removal of the liver. The present author paid especial attention to the early stages of tolylenediamine icterus. Unlike Kálláo, he found that dextrose does not inhibit bile formation, but contrary also to the observations of Rosenthal and his coworkers, he found that icterus occurs if the liver is absent. The degree of pigmentation of the blood serum is moderate in these animals, and bilirubinemia never becomes as marked as in animals with intact liver. The van den Bergh reaction, which theoretically should be of great help in determining what is happening during the early stages of the icterus, has little value because the reaction is interfered with by derivatives of tolylenediamine and also possibly pigments other than bilirubin, such as xanthochromes and precursors of bilirubin. During the early stages of the jaundice, in animals with intact liver, the thoracic duct lymph contains from two to three times as much bilirubin as the blood, indicating resorption of bile from the liver. Histologic examination of the liver at this early stage does not reveal the severe injury described by Rosenthal and his associates. Bile stasis can be detected in the intracellular bile canaliculi, and biliary thrombus formation has begun in the smaller interlobular ducts. The author concludes that in the beginning tolylenediamine icterus is hemolytic, but to only a slight degree; to a much greater degree it is obstructive and resorptive.

O. T. SCHULTZ.

HEALING PHENOMENA IN EXPERIMENTAL INFARCTION OF THE KIDNEY. U. SCHNAPAUFF, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:781, 1928.

This is a contribution, by a pupil of Aschoff, to the long controversy between the latter and Ricker over Aschoff's neurovascular theory of inflammation. Since Ricker had interpreted the phenomena occurring in the early stages of renal infarction in support of his theory, Schnapauff caused infarction of the kidney in rabbits by ligating one of the branches of the renal artery. The resulting changes were studied at intervals, beginning immediately after the ligation and continuing until complete healing of the infarct occurred. In the earliest stages, the presence of free red blood corpuscles in the peripheral zone of the infarct was the result of

diapedesis through inactive, mechanically distended capillaries, and the leukocytic infiltration in this zone was due to chemotaxis. Healing occurs by the ingrowth of fibroblasts from the periphery and not as the result of any neurovascular reactions in the infarcted tissue. The interpretation of the observations, which are those familiar to all, is in the terms of cellular pathology, not in those of Ricker's neurovascular "Relationspathologie."

O. T. SCHULTZ.

**PATHOLOGIC HISTOLOGY OF METRORRHAGIA.** O. TERASAKI, Beitr. z. path. Anat. u. z. allg. Path. **79**:819, 1928.

The author made a histologic study of the endometrium in ninety-two cases of intermenstrual hemorrhage. The material consisted in greater part of curettings and in smaller part of extirpated uteri. He divides his material into three groups: hemorrhagic metropathy of Aschoff, inflammatory endometritis of infectious origin and senile apoplexy of the uterus. Most of his material fell into the first group and consisted of eighty-one cases. These he subdivides into a subgroup of twenty cases in which the glandular changes of the endometrium could be correlated with the normal menstrual cycle but were abnormal in the time of their occurrence in the cycle. The age in this group varied from 35 to 53 years. In the second subgroup of sixty-one cases, the endometrial glands were hyperplastic, but the hyperplasia is held to be not cyclic but permanent, a true glandular hyperplasia. In forty-five of these cases the age ranged from 43 to 62 years, in six it was from 20 to 43 years, and in ten less than 20 years. In the metropathies the chief change was vasomotor, a capillary instability, in the words of the author, which manifested itself by hyaline capillary thrombosis and capillary hemorrhage. Small areas of necrosis were also present, but these were not due to capillary thrombosis. The gitter fibrils of the superficial layer of the endometrium remained intact. The changes occurring in women at and past the menopause are the result of abnormal prolongation of the menstrual cycle and of abnormalities in the sequence of portions of the cycle. Occurring as a prolongation of the menopause or, in younger women, associated with glandular hyperplasia, the metrorrhagia is due to abnormal ovarian function or to disharmony between general metabolism and ovarian function. There were only four cases of true inflammatory endometritis. The endometrium was infiltrated by lymphocytes, often by plasma cells, and proliferation of stroma and capillary endothelium was noted. The senile apoplexy group consisted of seven patients whose ages ranged from 56 to 88 years. The endometrium was atrophic, and the walls of the arteries of the myometrium were greatly thickened. The hemorrhage is a terminal affair in the life of the woman and is the result of passive capillary hyperemia.

O. T. SCHULTZ.

**FIBRO-ADENOMATOSIS CYSTICA MAMMAE.** CARL SEMB, Acta chir. Scandinav. (supp. 10) **64**:1, 1928.

One hundred and forty-four cases of fibro-adenomatosis mammae were studied after the glands were dissected from fat, fascia, muscular and cutaneous tissues. Multiple parallel cut surfaces and from ten to twenty blocks stained by various methods were submitted to examination.

Fourteen cases were observed in men. Here the tumor varied considerably in size but was usually more or less round and elastic, and the line of demarcation from the surrounding fat tissue was not quite sharp. Microscopically, there were epithelial-lined passages which were surrounded by newly formed connective tissue, and outside the latter was fibrous connective tissue. Nowhere were there any glandular alveoli. This cellular new formation was regarded as a hypertrophic growth of connective and epithelial tissue rather than as an inflammatory process or genuine tumor. Only one case showed cyst-formation similar to that found in fibro-adenomatosis cystica in women.

Fibro-adenomatosis simplex (microcystica) presents large or small thickenings of firm consistency in the mammary gland. These thickenings may be local or diffuse, with grayish-white or whitish tissue which is more or less sprinkled with

reddish-gray specks that represent cystically dilated acini surrounded by young connective tissue; the interlobular supporting connective tissue is varied in quantity. The assumption is made that this is a simultaneous fibro-epithelial proliferation, because in early cases Semb never noted proliferation of epithelial tissue without corresponding changes in the connective tissue. If the new formation of glands continues further, small, medium, or larger lobules are formed with numerous epithelial-lined cavities. Fibro-adenoma differs in that it is a circumscribed tumor containing only epithelium and connective tissue. Fibrolipo-adenoma and adenoma are distinguished by a sharply demarcated connective tissue capsule. Chronic mastitis presents a well defined inflammatory process. Hypertrophy of pregnancy, especially in the early months, may resemble fibro-adenomatosis, but in the former there is regular epithelial proliferation with pronounced secretory activity, and the connective tissue recedes into the background. Menstrual or periodic changes in the mammae may simulate fibro-adenomatosis, but in the latter the changes are far more pronounced and irregular. Diffuse fibromatosis (Reclus, Schimmelbusch) is regarded as an advanced stage of fibro-adenomatosis.

Fibro-adenomatosis cystica simulates the microcystic form, but in addition there are multiple, macroscopically visible cysts. These cysts may be lined by ordinary mammary epithelium and represent dilated acini, or by pale epithelium which may form papilla-like structures; lastly, there may be adenomatous papillomas with vascular connective tissue in the stroma. The latter condition is found in dilatations or cystic extensions of the large milk ducts. Retention of secretion seems to play an important part in the formation of cysts larger than a pea, whereas the formation of smaller cysts is mainly due to active proliferation of epithelium.

Inflammatory changes in fibro-adenomatosis (microcystic) does not seem to be an etiologic factor. In the glands with large cysts the round cell infiltration is regarded as secondary. Abscess near the nipple was observed in nine breasts, but such inflammatory changes were regarded as recent. Xanthoma cells were frequently found in cysts, connective tissue cells and carcinoma cells. In all of 101 preparations there were 6 in which there was a previous mastitis; its occurrence in such a small number rules it out as an etiologic factor and should be regarded purely as a coincidence.

Adenomatous papillomas occurred in the milk ducts in 27 per cent of the cases as multiple and varying sized tumors in the later stages of fibro-adenomatosis cystica. Fibro-adenoma was not found in connection with the earlier stages of fibro-adenomatosis, but was noted in the late stages and arose as a proliferation of a single milk duct in the form of fibro-epithelial new-formations. In only 2 per cent of the cases of fibro-adenomatosis (microcystica) was there any atypical growth; in fibro-adenomatosis cystica, however, 24 per cent of the cases presented atypical infiltrating tumor tissue. The material seems to indicate that there is no definite relation between the local purulent inflammation in fibro-adenomatosis and the development of cancer. In bilateral fibro-adenomatosis cystica there is a tendency toward bilateral primary carcinoma of the breast in that it occurred in 9 of the 23 cases. The microscopic examinations were not complete, however, in all those reported. From his work Semb concludes also that carcinoma can have a multicentric origin. In two patients there were bilateral mammary metastases from the stomach, which demonstrated that the cancer tissue had no power of producing any secondary proliferation of a fibro-adenomatous character. In 40 per cent of the cases of carcinoma there were fully developed pictures of fibro-adenomatosis cystica, and in a further 40 per cent various less pronounced or special forms of fibro-adenomatosis were detected; the remaining cases did not show definite signs of fibro-adenomatosis.

The etiology of fibro-adenomatosis is not clear. Trauma may be a factor in some cases. The initial stages occur about the middle of the period of sexual maturity in women. The greater number of the more developed forms are found shortly before the climacteric, a smaller proportion during and after the climacteric. Unmarried women are affected relatively more frequently, and the lesion is more

frequent in nulliparae. The figures in relation to abortions and lactation are not adequate and therefore not of significance. The greatest majority of women had normal menstruation. There is no connection with senile involution of the mamma. The clinical picture, prognosis and treatment are also given.

RICHARD A. LIFVENDAHL.

## Pathologic Chemistry and Physics

THE CONCENTRATION OF ACID AND BASE IN THE SERUM IN NORMAL PREGNANCY. H. C. OARD and J. P. PETERS, *J. Biol. Chem.* **81**:9, 1929.

Pregnancy may be accompanied by a decrease of approximately 5 per cent in the concentration of the basic cations available from the blood plasma. The authors offer no explanation of the decrease, but present an interesting and exhaustive discussion of its possible pathogenesis. The changes compensating for the decrease are described in detail.

ARTHUR LOCKE.

THE RELATION OF THE SERUM PROTEINS AND LIPIDS TO THE OSMOTIC PRESSURE. E. H. FISHBERG, *J. Biol. Chem.* **81**:205, 1929.

An extensive reduction in the concentration of protein available from the blood plasma, such as may accompany intensive hemorrhage, is followed by a compensatory lipemia, directed toward the restoration of a normal osmotic pressure.

ARTHUR LOCKE.

THE METABOLISM OF SULPHUR (CYSTINURIA). H. B. LEWIS and S. A. LOUGH, *J. Biol. Chem.* **81**:285, 1929.

A comparison of the quantities of cystine excreted by a patient with cystinuria during maintenance on cystine-poor and cystine-rich diets failed to indicate any impairment in the capacity of the subject to utilize this important amino-acid. The cystine voided during cystinuria would appear to be chiefly of endogenous origin.

ARTHUR LOCKE.

LIPID EXCRETION. W. M. SPERRY, *J. Biol. Chem.* **81**:299, 1929.

Dogs receiving an essentially lipid-free diet excrete a small but definite amount of lipids in the feces. The excreted lipids appear to be contained within the various cellular elements present: bacteria, desquamated epithelial cells, protozoans, etc., and do not necessarily represent the product of a secretion into the intestine.

ARTHUR LOCKE.

MICROSCOPIC AND X-RAY INVESTIGATIONS ON THE CALCIFICATION OF TISSUE. N. W. TAYLOR and C. SHEARD, *J. Biol. Chem.* **81**:479, 1929.

An optical study has been made of several types of calcification of tissue, including that of normal bone, of dental enamel and dentine, of rachitic bone, of bone low in phosphorus, of salivary calculus and of tuberculous lung. The conclusion is drawn that the solid inorganic phase consists essentially of very small crystals of apatite minerals of the general formula  $3\text{Ca}_3(\text{PO}_4)_2 \cdot \text{CaX}_2$ , in which  $\text{X}_2$  ordinarily represents  $\text{CO}_3$ ,  $\text{F}_2$ ,  $(\text{OH})_2$ ,  $\text{O}$ ,  $\text{SO}_4$  and  $\text{Ca}$ , which may to some extent be replaced by  $\text{Mg}$ . The index of refraction may serve as a measure of the degree of calcification of dried tissues, being low for bones and high for dental enamel and in certain cases of pathologic deposition. It is probable that the index is determined by the relative amounts of inorganic crystal and organic material in the unit structure. Diffraction patterns of x-rays obtained by the powder method have been obtained for apatite, dental enamel, normal bone, salivary calculus, tuberculous pulmonary calcification and synthetic tricalcium phosphate. The similarity of the patterns indicates a similarity of crystal structure. The conclusion is in agreement with that based on the optical evidence.

AUTHORS' SUMMARY.

BLOOD AS A PHYSICOCHEMICAL SYSTEM (DIABETIC COMA). D. B. DILL, A. V. BOCK, J. S. LAWRENCE, J. H. TALBOTT and L. J. HENDERSON, *J. Biol. Chem.* **81**:551, 1929.

An enormous amount of critically evaluated data has been condensed into a monograph presenting a "synthetic" description of the physicochemical character and behavior of the blood during diabetic coma.

ARTHUR LOCKE.

THE ALKALINE RESERVE AND OXYGEN CAPACITY OF ARTERIAL AND OF VENOUS BLOOD. L. M. HURXTHAL, A. V. BOCK, J. H. TALBOTT and D. B. DILL, *J. Biol. Chem.* **81**:681, 1929.

In a series of normal subjects at rest and at work, and in another series of pathologic subjects only small differences were found between arterial and venous blood both with respect to carbonic acid capacity at a partial pressure of 40 mm. of CO<sub>2</sub> and with respect to oxygen capacity.

AUTHORS' SUMMARY.

DISTRIBUTION OF ELECTROLYTES IN HEMOPHILIC BLOOD. R. V. CHRISTIE, J. SENDROY and D. D. VAN SLYKE, *Quart. J. Med.* **22**:65, 1928.

The chloride and bicarbonate distribution ratios in hemophilic blood are within the range of these ratios in normal blood, but in the lower half. Also the mechanism governing the distribution of electrolytes between cells and serum of hemophilic blood appears to be normal. This study was made on specimens of blood from a young male negro who was a hemophilic and gave a family history characteristic of that disease.

N. ENZER.

CHRONIC MERCURIAL POISONING. A. HERTZ, *Klin. Wchnschr.* **8**:541, 1929.

Among thirty-five patients with amalgam teeth fillings, thirty-four were found to be eliminating mercury, a result in general agreement with published reports, although the percentage is somewhat higher. This is perhaps explained by the fact that in most cases more mercury is found in the stools than in the urine, and others have analyzed only the urine.

AUTHOR'S SUMMARY.

## Microbiology and Parasitology

THE MONOCYTES IN ACTIVE TUBERCULOSIS. K. D. BLACKFAN and L. K. DIAMOND, *Am. J. Dis. Child.* **37**:233, 1929.

The degree of activity in tuberculosis is reflected in the peripheral blood of infants and of children. A high monocyte-lymphocyte ratio and the presence of epithelioid cells usually mean an active tuberculous infection. An increasing monocyte-lymphocyte ratio and the persistence of a high absolute monocyte count signify extension of the process. Reversal of the ratio (a fall in monocytes and an increase in lymphocytes) denotes healing lesions. In cases in which the diagnosis is questionable, a study of the blood by the supravital technic may lead to a correct diagnosis. When the diagnosis is established, supravital studies of the blood may be of prognostic value in indicating whether the lesion is progressing or undergoing regression.

AUTHORS' SUMMARY.

PULMONARY GANGRENE DUE TO SPIROCHETES AND FUSIFORM BACILLI. J. M. LEWIS and L. H. BARENBERG, *Am. J. Dis. Child.* **37**:351, 1929.

A case of pulmonary gangrene due to spirochetes and fusiform bacilli is reported in a child, aged 3 years. The presence of spirochetes and fusiform bacilli in smears taken directly from the larynx and from the fetid material obtained by lung puncture was instrumental in making the diagnosis. The importance of oral hygiene, prompt treatment of spirillar infections of the mouth and good nutrition in the prevention of fusospirochetal pulmonary gangrene is emphasized.

AUTHORS' SUMMARY.



VARICELLA COMPLICATED BY ACUTE NEPHRITIS: REPORT OF A CASE ASSOCIATED WITH STREPTOCOCCAL INFECTION OF THE TONSILS. E. RANKIN DENNY and B. M. BAKER, JR., *Bull. Johns Hopkins Hosp.* **44**:201, 1929.

A case of focal glomerular nephritis occurring early in the course of hemorrhagic varicella is reported. The onset of the nephritis, and the recovery from this complication paralleled the course of a complicating acute tonsillitis due to hemolytic streptococci, of the B type. The organisms isolated from the tonsils and urine had common cultural characteristics. During the acute stage of the nephritis, hemolytic streptococci of B type were found in the urine, while after recovery from the nephritis they disappeared from both the throat and the urine. It is suggested that the acute hemorrhagic nephritis in this case was associated not with hemorrhagic varicella but with the streptococcal infection.

AUTHORS' SUMMARY.

HETEROGENEITY OF STREPTOCOCCI FROM SPUTUM. SANFORD BURTON HOOKER and LILLIAN M. ANDERSON, *J. Immunol.* **16**:291, 1929.

Alpha streptococci, which predominate in minor respiratory infections, are of such extraordinary cultural and antigenic diversity even in the secretions of an individual patient, that they may almost certainly be excluded as primary pathogenic invaders; their rôle here as actual secondary agents of infection is probably very subordinate. Comparison of these organisms, which in plates give a fictitious impression of homogeneity, with the streptococci and other bacteria associated with more entitative types of disease, and whose actual cultural and antigenic homogeneity in the individual is strongly supported by the evidence available, has led to the formulation of this criterion of a primary microbial pathogen in a given individual: Multiple selections from the dominant colony type should show a high proportion of essentially indistinguishable strains. The changeable differences due to dissociative phenomena should be excluded. The beneficial reactions attributed to the "autogenous" vaccine treatment of bronchitis are probably not often mediated by a specific immunologic mechanism. A comprehensive classification of alpha streptococci cannot be achieved by current methods without an expenditure incommensurate with its probably limited value to the medical profession.

AUTHORS' SUMMARY.

REACTIONS OF GUINEA-PIGS TO VIRUS OF ENDEMIC TYPHUS FEVER. KENNETH F. MAXEY, *Pub. Health Rep.* **44**:589, 1929.

Blood from persons sick with the "endemic typhus" of southeastern United States injected into guinea-pigs produces a definite febrile illness, with recovery and subsequent immunity to reinoculation. The reaction of the guinea-pig appears to be identical with that produced by Mexican typhus, according to Mooser's description. It differs from that of the Old World typhus (1) in regard to the character of the fever curve, (2) in the relative rarity of the so-called typhus nodes in the histologic preparation of the brain, and (3) in the presence of an obvious and well defined scrotal lesion first described by Neill, in 1918, in Mexican typhus.

So far as the differences in the temperature curve and in the relative frequency of occurrence of typhus nodes are concerned, these might be explained as due to strain variation. In a study of thirteen strains obtained from cases in the same general locality in Poland, Hach found one strain in which, in spite of a very outspoken febrile reaction, the brain lesions were extremely hard to find. In another the temperature elevations were relatively slight, although the period of incubation and duration of the fever were essentially the same as in other strains.

On the other hand, the involvement of the scrotum is much more striking and extensive than has been observed or described in guinea-pigs inoculated with Old World typhus. When this obvious involvement was first encountered in a strain obtained from a case in Montgomery, Ala., in 1925, it was thought possible

that it might be due to a secondary or contaminating infection. Since that time the same condition has been present in three other strains which have been successively established from cases in Montgomery, Ala., Savannah, Ga., and Wilmington, N. C. It was observed by Dr. William Allan in a strain from a case in Charlotte, N. C. It has been constantly associated with the presence of the virus and not with other infections in guinea-pigs. It has not been observed during the past two years in guinea-pigs from the same stock which have been inoculated with two strains of Old World typhus, though much less extensive histologic changes of a similar nature occur.

These observations have been so consistent that it seems to be established that the obvious involvement of the scrotum and the rarity of brain lesions are characteristic of the endemic typhus virus in guinea-pigs as they are of Mexican virus. The demonstration of rickettsia-like organisms in the epithelial cells of the tunica brings additional evidence as to their identity. It appears, therefore, that a North American strain of typhus can be recognized and distinguished from Old World typhus, though the two be closely related immunologically.

The conclusion may be drawn that the disease which is endemic in our eastern seaports, Wilmington, N. C., Charleston, S. C., Savannah, Ga., Jacksonville, Fla., belongs to the typhus group, but is not dependent on importation from across the sea. This disease has a common origin with the typhus of Mexico, even though transmission be effected by some agent other than that generally recognized for this disease, namely, the louse.

AUTHOR'S SUMMARY.

THE EXHAUSTION OF MEDIA IN BACTERIAL CULTURE. J. C. BROOM, *Brit. J. Exper. Path.* **10**:71, 1929.

The power of fruit juice in aiding the regrowth of an organism on an agar slope on which the organism has already been grown for some days is dependent, not on its vitamin content, but on the presence of carbon compounds which the organism can assimilate. The inhibition of the growth of one bacterium by another may be caused by a deficiency of available carbon due to the original growth. This explains why bacteria with greater powers of fermentation inhibit those which are less active in this respect.

PEARL ZEEK.

THE INFLUENCE OF COMPLICATIONS ON THE COLLOID LABILITY IN PULMONARY TUBERCULOSIS. L. HANTSCHMANN and M. STEUBE, *Beitr. z. Klin. d. Tuberk.* **70**:536, 1928.

In 200 patients with pulmonary tuberculosis, the sedimentation rate and the protein fractions were determined. The deviations of the latter are not proportional with the sedimentation rate. Extrapulmonary tuberculosis and inflammatory diseases increased the sedimentation rate and the globulin fraction beyond the degree that could be expected on account of the pulmonary lesion. Circulatory disorders, liver diseases, endocrine and constitutional disturbances caused at times a relatively decreased sedimentation rate.

MAX PINNER.

THE COURSE OF GENITAL TUBERCULOSIS IN THE PREGNANT, PUERPERAL AND ALLERGIC ANIMALS. J. GRANZOW, *Beitr. z. Klin. d. Tuberk.* **70**:548, 1928.

In all these experiments tubercle bacilli were injected into one horn of the guinea-pig uterus. It was found that uterine lesions developed in 6 per cent of normal uteri, in 28 per cent of pregnant uteri, in 45 per cent of puerperal uteri, and in 50 per cent if a subcutaneous primary infection had preceded the intra-uterine infection. The survival period was shortened in animals which were in the pregnant or the puerperal stage. The uterine lesions produced by local infection may occur anywhere within the uterine cavity. The peripheral layers are more frequently diseased than the central layers. The histologic picture of uterine tuberculosis is frequently atypical. Following an intra-uterine reinfection,

acute endometritis may develop. After uterine infection a number of nonspecific alterations may occur in this organ. They may be degenerative, inflammatory, disturbances of the circulation or marked atrophy of the whole organ. An ascending tuberculosis of the tubes was never observed, neither were the ovaries infected. Pregnancy is almost always interrupted by uterine infection. This mode of infection almost always produces sterility. Coincident with uterine lesions, the regional lymph glands are almost always diseased. If no uterine lesions are found the regional lymph glands may still be tuberculous. In puerperal animals the entire lymphatic system shows more pronounced lesions than in normal animals, while the lungs appear less affected.

MAX PINNER.

THE PATHOGENESIS OF TUBERCULOUS MENINGITIS IN CHILDHOOD. D. VON WANGENHEIM, Beitr. z. Klin. d. Tuberk. **70**:670, 1928.

The frequency of tuberculous meningitis in children at the age of from 1 to 3 years is probably due to the fact that at this age extensive caseation of bronchial lymph glands is particularly frequent. Measles, whooping cough, clinically active tuberculosis and trauma do not seem to play an important rôle in the development of the disease. Occult tuberculosis seems to be more important. Vaccination and heliotherapy are some times suggestive as causative factors. In about 50 per cent of the patients, the tuberculin reaction was positive eight days before death, which proves that a decrease of allergy is not a necessary condition for the development of generalization. Extrafamilial infection is twice as frequent as intrafamilial. Primary pulmonary foci were found in 95 per cent of the cases. Their localization does not seem to play a significant rôle in the development of meningitis. The focus from which generalization occurs is most frequently a caseated focus in bronchial lymph nodes. In 12 per cent of the cases, solitary tubercles in the brain were found. Intima tubercles in the pulmonary veins are rare. Their localization and structure argue against Weigert's theory, and favor the opinion of Liebermeister and Huebschmann, according to whom generalization occurs, not by the rupture of a vascular focus, but by bacillemia maintained by an extravascular focus.

MAX PINNER.

THE PATHOLOGIC ANATOMY OF PULMONARY INFILTRATIONS. H. RUBINSTEIN, Beitr. z. Klin. d. Tuberk. **70**:773, 1928.

A child was diagnosed as having an interlobar empyema. A rib resection was done and the pleural cavity was opened, but no exudate was found. A solid subpleural nodule was felt in the right middle lobe. Small pieces were excised for histologic diagnosis. After the operation, the child made a good recovery and the roentgenologic shadows disappeared almost completely. Both the clinical course and the histologic studies showed that the process was a tuberculous infiltration of the pulmonary tissue. The sections showed densely infiltrated lung tissue, the presence of tubercle bacilli, small necrotic foci, giant cells and diffuse proliferation of connective tissue. These observations show, too, that tuberculous infiltrations may be absorbed to a large extent.

MAX PINNER.

ACUTE DIFFUSE ENCEPHALITIS IN STREPTOCOCCUS ENDOCARDITIS. P. KIMMELSTIEL, Beitr. z. path. Anat. u. z. allg. Pathol. **79**:39, 1928.

The term endocarditis lenta should be limited to those cases of subacute bacterial endocarditis due to *Streptococcus viridans*. This form is characterized by infrequent occurrence of septic emboli which go on to abscess formation. In a few cases the presence of embolic abscesses within the brain has been reported. Purulent meningo-encephalitis of the brain has also been described. The author records eleven cases of subacute bacterial endocarditis due to *Streptococcus viridans*, in which there was diffuse involvement of the brain without abscess formation. The process was in part a degenerative one, consisting of areas of softening, which

the author considers ischemic in origin, and in part of a reactive inflammatory nature characterized by glial proliferation. The author believes such a diffuse nonpurulent encephalitis to be a not infrequent terminal process in viridans endocarditis.

O. T. SCHULTZ.

POSTVACCINAL ENCEPHALOMYELITIS. P. SCHÜRMANN, Beitr. z. path. Anat. u. z. allg. Pathol. **79**:409, 1928.

Although postvaccinal encephalomyelitis has shown a decided increase since 1922 in England and Holland, where the condition has been carefully studied histologically, the author claims that there are no previous reports of histologic studies in the German literature. The two cases studied by him occurred in children, aged 8 years and 18 months, respectively. The characteristic change noted by him was a zone of demyelination about the dilated veins, usually at the junction of white and gray matter. Proliferation of glia was also noted. The changes occurred in both brain and cord. In the older child, in whom the vaccination was complicated by numerous furuncles in the axillae and on other parts of the body, there was infiltration by lymphocytes and large mononuclear cells about some of the veins, in addition to the more characteristic demyelination. In his discussion of the nature of the process, the author does not accept the view of Luksch that the involvement of the nervous system is directly due to the vaccine virus. Perhaps the latter prepares the ground in susceptible persons for changes which are the result of nonspecific toxins. Schürmann holds the encephalomyelitis following vaccination to be identical histologically with that which may follow measles.

O. T. SCHULTZ.

THE RELATION OF OXIDIZING SUBSTANCES IN BACTERIA AND YEASTS TO CELLULAR OXIDASES. W. LOELE, Virchows Arch. f. path. Anat. **267**:733, 1928.

The author studied the granules that could be demonstrated in bacteria with paraphenylendiamine, with or without  $\alpha$ -naphthol. *M. catarrhalis* could be readily distinguished from other throat organisms by this reaction. Oxidizing substances were shown in yeast cells by means of the peroxidase reaction with benzidine. The granules appeared variously colored, depending partly on the age of the culture, and were either diffuse or localized in some structure of the cell. The oxidizing substances in bacteria were bound to various structures, mostly to lipoids. The presence of oxygen was essential to the formation of these substances, but they could be formed only by certain types of organisms. The presence of iron appeared to influence favorably the oxidase reaction in yeast cells. The oxidases were found to be complex bodies, with oxidizing, lytic and pigment-forming properties, possibly related to nucleolar substance. Similarity was shown between bacterial and cellular oxidases in several respects.

B. R. LOVETT.

TUBERCULOSIS INFECTION AND TUBERCULOSIS VACCINATION. J. HEIMBECK, Ztschr. f. Tuberk. **52**:378, 1928.

Pirquet reactions were done on more than 2,000 persons of all ages in Norway. The results showed that only a minority of children was infected with tuberculosis, and that the most important period of infection must be between 15 and 20 years of age. These studies led to the conclusion that tuberculous disease at adult age is usually a direct consequence of the primary infection, and is not caused by a latent childhood infection. A latent childhood infection seems to afford a fair protection against later infections. A number of adults and children with negative Pirquet reactions were given injections subcutaneously with B.C.G. vaccine. They developed a tuberculin allergy. Observations on vaccinated and nonvaccinated nurses led to the conclusion that this B.C.G. allergy affords the same immunity as a benign natural infection.

MAX PINNER.

## Immunology

**HYPERSENSITIVENESS TO DIPHTHERIA BACILLI.** JAMES M. NEILL, WILLIAM L. FLEMING and EMIDIO L. GASPARI, *J. Infect. Dis.* **44**:150, 1929.

In this study of the skin reactions to injections of diluted diphtheria culture filtrate, a group of 1,350 adults was tested with injections of  $8 \times 10^{-4}$  cc. of heated (80 C.) filtrate, and of the same amount of broth culture medium. Immediate reactions that could be referred to the diphtheria bacterial derivatives occurred in only four persons, 0.3 per cent of the group. Reactions to injection of the test dose of diluted broth, on the other hand, were common, significant ones being observed in 18 per cent of the group. Most of the responses to the injection of diluted broth could be referred to actual constituents of broth, but some reactions were apparently due to trauma alone. A general outline is given by which the skin reactions to intradermal injections of the whole bacterial filtrate may be distinguished.

AUTHORS' SUMMARY.

**THE PROTEINS OF EGGWHITE.** LUDVIG HEKTOEN and ARTHUR G. COLE, *J. Infect. Dis.* **44**:165, 1929.

Tests made with the precipitin reaction indicate that crystallized ovalbumin, when subjected to putrefactive processes, is not converted into conalbumin. It has also been shown that such a putrefying solution of ovalbumin loses its power to react with its specific antiserum even while it still contains a considerable amount of coagulable protein.

AUTHORS' SUMMARY.

**IMMUNE REACTIONS TO ACID TREATED BACTERIA.** ORAN I. CUTLER, *J. Infect. Dis.* **44**:203, 1929.

Bacteria treated with chemicals appear to lose the ability to incite antibody production in close proportion to their loss of power to produce immunity. When immunity to live typhoid bacilli was demonstrated, agglutinins for the organisms were also found, at least in low titer. Bacteria which are not completely destroyed by chemicals with which they are treated may be changed so that new antigens are formed, to which rabbits respond by the production of antibodies specific for the altered bacteria. Antibodies formed for typhoid bacilli treated with nitric acid, which were different from those formed for live organisms, were not demonstrated to be bactericidal for live bacteria. The antibodies formed for typhoid bacilli treated with second-normal acid appear to be the same whether nitric, hydrochloric, sulphuric or acetic acid is used.

AUTHOR'S SUMMARY.

**PASSIVE TRANSFER OF HYPERSENSITIVENESS TO DIPHTHERIA BACILLI.** JAMES M. NEILL and WILLIAM L. FLEMING, *J. Infect. Dis.* **44**:224, 1929.

The three types of skin reaction to diphtheria bacterial derivatives are differentiated in this paper by passive transfer experiments. The capacity for the immediate hypersensitive reaction to heated diphtheria filtrate was transferred to 61 to 103 persons by the Prausnitz-Küstner technic; the capacity for the delayed or pseudo reaction to the same heated filtrate failed of transference. Serum from persons without the pseudo reaction had no neutralizing effect when previously injected into the skin of persons with pseudo reactivity, serum from a person with a negative Schick reaction transferred local antitoxic immunity to skin areas of persons with positive Schick reactions, as indicated by neutralization of toxin injected two days after introduction of the serum.

The success or failure of the Prausnitz-Küstner technic to transfer to local skin areas the types of antidiphtheria immunity represented by the three different skin reactions is illustrated. The results showed that active antidiphtheria immunity had no relation to a person's response in the passive transfer of the immediate skin reaction to the culture filtrate of the same bacteria.

AUTHORS' SUMMARY.

ANTICOMPLEMENTARY POWER OF HEPARIN. ENRIQUE E. ECKER and PAUL GROSS, *J. Infect. Dis.* **44**:250, 1929.

Heparin inhibits hemolysis *in vitro* in the hemolytic system. This is the result of action on complement rather than on cells. The heparin-inactivated complement can be reactivated by the addition of heat-inactivated human or guinea-pig serum. Thus, it is inferred that the action of heparin is on the third or fourth component of the complement. The facts that NH ammonia-complement reactivates heparin-inactivated complement and that guinea-pig serum inactivated by cobra venom fails to reactivate heparin-inactivated complement point to the conclusion that the action of heparin is on the third rather than the fourth component. The anticomplementary power of heparin is not clearly demonstrable *in vivo*, in spite of highly anticoagulant properties. This fact, together with the demonstrated influence of the chlorides of calcium, magnesium and lithium, indicates that the anticomplementary and anticoagulant properties of heparin depend on separate mechanisms. The experiments plainly show that heparin operates on complement, but ancillary action on amboceptor cannot be excluded.

AUTHORS' SUMMARY.

EFFECT OF MULTIPLE INJECTIONS OF DIFFERENT MATERIALS ON THE RETICULO-ENDOTHELIAL SYSTEM AND ON THE IMMUNITY RESPONSE. KATHARINE M. HOWELL and DOROTHY A. BEVERLEY, *J. Infect. Dis.* **44**:298, 1929.

The histologic examination of tissue, after the injection of multiple nonprotein foreign material, suggests the probability that the proliferation of reticulo-endothelial cells is so stimulated and so rapid that complete blockade of the reticulo-endothelial system cannot be attained.

AUTHORS' SUMMARY.

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI AND RAGWEED POLLEN. WILLIAM L. FLEMING and JAMES M. NEILL, *J. Infect. Dis.* **44**:308, 1929.

The investigation consisted of a quantitative correlation of the responses of a group of people to ragweed pollen extract, in skin locally sensitized by ragweed hypersensitive serum, with the responses of the same persons to diphtheria culture filtrate in skin locally sensitized by diphtheria hypersensitive serum. Proper quantitative relationships between serum and test substance were established by preliminary experiments. The final tests for comparison were made on sixty-four persons. When the pollen-antipollen and bacterial-antibacterial systems were properly adjusted, the skin response of each person to one antigen was approximately the same as his response to the other; in most cases, they were identical. The quantitative correspondence in the individual transfer responses to the bacterial and nonbacterial antigen is illustrated. The results were discussed both from the standpoint of their significance in the study of diphtheria bacterial hypersensitiveness and from the standpoint of their theoretical interest in the study of hypersensitiveness in general.

AUTHORS' SUMMARY.

HISTAMINE IN RELATION TO CUTANEOUS HYPERSENSITIVENESS. JAMES M. NEILL, WILLIAM L. FLEMING and LURLINE V. RICHARDSON, *J. Infect. Dis.* **44**:321, 1929.

The individual variations in the response of normal skin to histamine were studied in thirty persons who had previously shown individual differences in responsiveness to antigens injected into specifically sensitized skin. Differences in reactivity to histamine were exhibited by the normal skin, but there was no correlation between the degree of responsiveness of the normal skin to histamine, and the responsiveness of the sensitized skin of the same person to injection of specific antigens. This lack of correlation is discussed from the standpoint of the usually accepted explanation of the mechanism of hypersensitive reactions.

AUTHORS' SUMMARY.

ANTI-VACCINAL SERUM. C. H. ANDREWES, J. Path. & Bact. **32**:265, 1929.

Generalized lesions appeared on the skin of 79 per cent of rabbits inoculated intradermally with a testicular strain of neurovaccine. This generalization could be prevented by giving comparatively small doses (3 cc.) of immune serum intravenously. Generalized lesions always appeared on the skin of rabbits inoculated intravenously with more than 500 skin-infecting doses of neurovaccine. Here also generalization could be prevented by giving intravenous serum before or mixed with the virus. With the serums used, approximately 1 cc. was necessary for every 1,000 m. i. d. of virus. Fifty-five per cent of the rabbits in which the serum prevented generalization were found on subsequent test to have developed an active immunity. Serum which reaches the tissues five minutes before the virus is far more effective than when the virus is five minutes ahead of the serum. This is most easily shown by "local passive immunity" experiments in the rabbit's skin.

AUTHOR'S SUMMARY.

THE SCHICK REACTION AND CIRCULATING ANTITOXIN. A. T. GLENNY and HILDA WADDINGTON, J. Path. & Bact. **32**:275, 1929.

Tolerance for diphtheria toxin may be determined by the intracutaneous injection of multiples of the Schick dose. Large reactions may be avoided by the use of toxins so chosen that the specific toxicity of the dilutions used is the same as that of the routine Schick dilution but the combining power is greater. A concentration of antitoxin in the blood of 1/250 unit per cubic centimeter of serum corresponds to the Schick negative level in guinea-pigs. In passively immunized guinea-pigs, this correspondence is not reached until equilibrium is reached between the circulation and tissues many hours after the injection of serum.

AUTHORS' SUMMARY.

IMMUNIZATION AGAINST CHICKENPOX. F. BENINI, Riv. di clin. pediat. **26**:824, 1926.

Benini gives his experiences with vaccination against chickenpox. He employed vaccination in forty cases, in twenty-seven using the scarification method and in thirteen intradermal inoculation with the lymph. He concludes that vaccination against chickenpox, if carried out with great care, is absolutely harmless. Prophylactic vaccination makes it possible to limit the spread of the disease. The best results are secured by employing the intradermal route. If chickenpox were always the mild disease that it is commonly, vaccination might be said to have chiefly an academic or scientific interest, but the fact is that the disease is not always benign but often takes on a nature dangerous to life, particularly in hospitals and gouttes de lait in which the patients are in a condition of lessened resistance.

ALLERGY OF THE TUBERCULOUS RABBIT AFTER SUPERINFECTION OF THE MESENTERY, CONJUNCTIVA AND CUTIS. H. H. KALBFLEISCH, Beitr. z. Klin. d. Tuberk. **70**:465, 1928.

In the first communication (*Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie* **78**:187, 1927), it was shown that the injection of tubercle bacilli causes local alterations in the circulation which vary with the amount of bacilli injected. These alterations secondarily cause changes in the tissue. The particularities of these processes are independent of the specific type of stimuli, but they are dependent on the degree of the stimuli. The same as in the first paper, an attempt is made in this study to prove the correctness of Ricker's "Relationspathologie" on the special example of tuberculous infection and reinfection. It is impossible, in a brief abstract, to report the author's experiments and arguments. Some of his most important conclusions are as follows: The processes caused by a tuberculous reinfection show certain deviations from those of a primary

infection only in animals with far advanced tuberculosis and not in animals with slight lesions. These deviations are caused by changed irritability of the nerves of the circulatory system. Far advanced tuberculous animals exhibit this changed irritability not only toward a specific reinfection but toward other stimuli as well (epinephrine). Therefore, the term "allergy" loses its meaning and should (with the term, tuberculosis immunity) be dropped from discussions of tuberculosis. The so-called "allergic reaction" indicates only severe disease. The local reaction of tuberculous superinfection is nonspecific. The "Koch phenomenon" is not an immunity reaction. Infection and reinfection, each being a nonspecific process, are distinguished only by circulatory alterations of varying degree.

MAX PINNER.

GLANDULAR REACTIONS FOLLOWING INJECTIONS OF OLD TUBERCULIN IN TUBERCULOSIS IN GUINEA-PIGS. K. G. LEDERMANN, *Beitr. z. Klin. d. Tuberk.* **70**:627, 1928.

In experimental tuberculosis of guinea-pigs, injections of tuberculin produce frequently an acute swelling of lymph glands particularly of those near the site of injection. This reaction is at times more sensitive, but less specific than the skin reaction. After repeated injections of tuberculin, the glandular reaction increases in intensity. Macroscopically unaltered glands react more frequently than macroscopically diseased glands.

MAX PINNER.

ACTION OF TUBERCULOUS ANTIGEN AND ANTIBODY ON A SURVIVING VASCULAR PREPARATION OF TUBERCULOUS GUINEA-PIGS, AND ITS PRACTICAL SIGNIFICANCE. U. RABBIOSI, *Beitr. z. Klin. d. Tuberk.* **71**:229, 1929.

Surviving vascular preparations from tuberculous guinea-pigs reacted with a vascular dilatation on perfusion with bacillary products such as bacillary emulsion or old tuberculin, while similar preparations from normal guinea-pigs reacted with a contraction. Serum from tuberculous patients, too, produced a vascular dilatation, but not, as a rule, in preparations from normal guinea-pigs. The author believes that the technic, which is described in detail, may be adapted for practical diagnostic purposes.

MAX PINNER.

LOCAL IMMUNIZATION AGAINST TUBERCULOSIS. K. W. CLAUBERG, *Beitr. z. Klin. d. Tuberk.* **71**:263, 1929.

Guinea-pigs were given intrapulmonary injections of various preparations of tubercle bacilli. Some time later they were infected by the same route with virulent tubercle bacilli. It appeared that some degree immunity had been produced.

MAX PINNER.

THE EFFECT OF ROENTGEN RAYS ON SPECIFIC IMMUNE BODIES. ALEXANDER LUSZTIG, *Centralbl. f. Bakteriologie* **105**:142, 1928.

Lusztig finds that exposure of animals to roentgen rays may have various effects on antibody production, depending on the intensity of the radiation, the antigen used and the time of application of the rays with respect to the time of injection of the antigen.

PAUL R. CANNON.

THE PROPERTIES AND MODE OF ACTION OF ANTHRAX-IMMUNE SERUM. ALFRED PETTERSSSEN, *Centralbl. f. Bakteriologie* **106**:294, 1928.

Petterssen asserts that anthrax-immune serum contains agglutinins, precipitins and complement-fixing antibodies but no bacteriolytic or opsonic ones. He believes, on the basis of experiments described in this paper, that in the animal body the anthrax bacilli form negatively chemotactic substances, these being particularly concentrated in the edema fluid. Immune serums contain substances which



neutralize these negatively chemotactic materials, thus allowing leukocytes to infiltrate and phagocytize the organisms. The virulence of the bacilli, then, depends on their ability to form these leukocyte-repelling substances; consequently, the virulence can be increased only by animal passage.

PAUL R. CANNON.

THE SIGNIFICANCE OF THE RETICULO-ENDOTHELIAL APPARATUS IN INFECTIONS.

J. L. KRITSCHESKI and L. SCHWARZMANN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **56**:322, 1928.

The reticulo-endothelial system does not act, or only to a minor extent, as a protective apparatus in infections with *Trypanosoma gambiense*. There was no evidence of any protective action in *Schizotrypanum cruzi* and *Spirochaeta morsus muris*.

W. C. HUEPER.

THE ANTIVIRUS OF BESREDKA IN EXPERIMENTAL STREPTOCOCCUS INFECTIONS.

H. DOLD and H. R. MÜLLER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **56**:347, 1928.

The growth inhibiting action of sterile filtrates of old, repeatedly inoculated bouillon cultures (antivirus of Besredka) can be explained satisfactorily by exhusation of the culture medium and the accumulation of specific inhibitory metabolic products. The inhibitory quality of *Streptococcus antivirus* is heat resistant. It is almost atoxic for rabbits. Rabbits could not be immunized by injections of *Streptococcus antivirus* against fatal streptococcus infections (virulency type III). The local reaction could be decreased and the life lengthened by several days through preceding intracutaneous injections with antivirus. The same results, however, were obtained by injections of bouillon and physiologic solution of sodium chloride. Similar results were seen in streptococcus infection of the virulency type II thus treated. Simultaneous injections of antivirus, bouillon or physiologic solution of sodium chloride, respectively, and infecting streptococci (virulency type II) had an unfavorable effect evidenced by the more marked local reaction and the lengthening of the disease. The results obtained by intracutaneous injections or local applications on infected lesions for therapeutic purposes gave varying results. Failures were frequent. As the antivirus acts as an inflammation-producing agent the best results were obtained by its prophylactic use twenty-four hours preceding the infection. The results were less reliable and less marked if the antivirus was used twenty-four hours after infection. The inflammation-producing action of injections of antivirus, as well as of bouillon and physiologic solution of sodium chloride, are due to the resulting injury of the tissue. The authors deny the existence of an antivirus which, according to Besredka, represents a split product of bacteria with a special affinity to the cells of the skin.

W. C. HUEPER.

THE NORMAL AND NONSPECIFICALLY ALTERATED BACTERICIDAL POWER OF THE SERUM. W. PFANNENSTIEL, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **56**:389, 1928.

The bactericidal power of the serum could be lowered in test tube experiments by various means (heat, irradiation with ultraviolet rays,  $p_H$  changes, changes in mineral content, addition of absorbents, etc.) due to changes in the colloidal status of the proteins and lipoids. The physicochemical status of the serum in the animal decides its bactericidal power. Changes in its content of mineral and dissolved cellular substances are effected by leukocytes, histiocytes, platelets and probably also cells of the reticulo-endothelial system. The physicochemical and chemical structure, especially lipid content, of the bacterial to be tested is also important in regard to the bactericidal action. Gram-positive bacteria, if susceptible to the bactericidal serum, succumb to it more easily than gram-negative ones. The normal

bactericidal quality against typhoid bacteria varies with different animals and in the individual with the different physiologic and pathologic conditions. Changes in the bactericidal "serum-status" can be produced in vivo by various nonspecific means resulting in disturbances of the physicochemical balance of the blood and alterations of the cellular colloids, especially of the reticulo-endothelial system and the autonomous vegetative system. Changes in the bactericidal power, which may be marked, are usually only temporary and of short duration. An increase of longer duration after injections is apparently rare and follows only substances which are not readily excreted as metals, rare earths, acetylsalicylic acid and the like. Alimentary influences, especially the introduction of vitamins, and pregnancy may produce long lasting increases of the bactericidal quality of the serum. Variations depend apparently on the exchanges of substances between the blood and the tissues, in which the reticulo-endothelial system plays an important part. Vascular dilatation effects an increase, vasoconstriction a decrease of the bactericidy due to changes in the permeability of the vascular wall. Decrease of the dispersion of the blood colloids increases the bactericidal power, while it is lowered by increase of the dispersion. The increase of calcium magnesium and potassium with simultaneous decrease of sodium in the blood results in an increase of the bactericidal qualities; the increase of sodium with simultaneous decrease of calcium and potassium produces a decrease of them. Weak acids increase the bactericidal qualities, weak bases have no effect. Incompensated acidosis, as present after parenteral injections of proteins, diminishes the bactericidal power. The subsequent excessive compensatory activity of the cells overcomes this injurious effect. Fever increases the bactericidy. The poisonous effect of metals, especially arsphenamine and acetylsalicylic acid, on the capillaries results in an increase of the bactericidal qualities. The sterilizing effect of chemical therapeutics depends also on the active participation of the cells, especially those of the reticulo-endothelial system.

W. C. HUEPER.

IMMUNOLOGIC SPECIFICITY OF SERUM CONSTITUENTS SEPARATED BY AN "ELECTRO-OSMOTIC" METHOD. R. OTTO and K. IWANOFF, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **57**:19, 1928.

Serum fractionated by an "electro-osmotic" method gave results in general conformity with those reported in the literature for serum fractionated by the usual methods. The globulin and albumin fractions proved specific in active anaphylaxis experiments; euglobulin and pseudoglobulin usually, but not always, could be distinguished from each other; the soluble and insoluble albumin fractions were less specific. Species specificity obtained in passive anaphylaxis experiments with the antisera of most of the serum fractions.

R. C. AVERY.

ANTIGENICITY OF LIPOIDS. S. JERMOLJEW, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **57**:102, 1928.

Ether extracts of egg yolk possessed antigenic properties; cholesterin and lecithin did not. Activation with hog serum changed cholesterin and lecithin from haptines to typical antigens. Separate injection of serum and the lipoids gave negative results.

R. C. AVERY.

A BIOLOGIC HOMOLOG OF HUMAN SPERMATOOA. N. J. ROSANOW, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **57**:164, 1928.

The antisera of rabbits and women immunized with the spermatozoa of other animals (ox, horse, hog, dog, cow, rabbit, guinea-pig) checked the motility of the antigen-spermatozoa, but had no influence on human spermatozoa. In contrast, the serum of rabbits immunized with ape spermatozoa proved heterospermatoxic to human spermatozoa.

R. C. AVERY.

THE RICKENBURG-BRUSSIN REACTION IN HUMAN RELAPSING FEVER. W. M. ARISTOWSKY and E. P. SCHAEETER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **57**:347, 1928.

The Rickenburg-Brussin reaction (adhesion of spirochetes to blood platelets) observed by others with serum of infected animals was obtained with serum from a patient locally infected with a culture of *S. recurrentis*. The reaction was given by either serum or plasma from blood drawn on the day following the fall in temperature; with their patient high serum dilutions (1:1,000) were effective. The blood platelets used in the test must be obtained from a healthy rat, guinea-pig or rabbit, but not from man. They suggest that their results indicate that the antibodies responsible for the adhesion phenomenon are identical with spirochetolysins.

R. C. AVERY.

ISOLATION OF GROUP SPECIFIC AGGLUTINOGENS OF HUMAN ERYTHROCYTES. C. HALLAUER, *Schweiz. med. Wchnschr.* **59**:121, 1929.

In confirmation of the work of Schütz and Wöhlisch, Hallauer found it possible to remove the specific agglutinogens from human erythrocytes by repeated washing with isotonic salt solution. Group B agglutinin was more readily removed than that of group A. In the case of group AB erythrocytes, the B agglutinin could be completely washed out, the remaining A component causing the corpuscles to react like those of group A. Working more particularly with groups A and B, Hallauer found that the washings of group A erythrocytes caused a flocculent precipitate in the presence of group B serum; Group B corpuscle washings yielded a similar precipitate with group A serum. When rabbits were immunized with the washings of group A or group B erythrocytes, there was obtained an anti-serum which agglutinated specifically its homologous corpuscles and had only slight activity for erythrocytes of heterologous groups. With such antisera it was possible to cause passive sensitization of guinea-pigs, death from anaphylactic shock resulting when the homologous erythrocytes were later injected. That death was not due to intracapillary agglutination was proved by the fact that no ill effects occurred if antiserum and corpuscles were injected within fifteen minutes of each other; a latent period between antiserum and corpuscle injection was necessary if death occurred, such a latent period being the criterion of the passive anaphylaxis experiment.

O. T. SCHULTZ.

ISO-ANTIBODIES IN MOTHER AND FETUS. NILE LIEBERG, *Acta path. et microbiol. Scandinav.* **6**:1, 1929.

The blood groups of 200 mothers and their 200 new-born infants were determined. In 116 children the groups were the same as in the mothers; in all children the receptor was qualitatively determined at birth, while the iso-agglutinin was present in only 60. In seven children agglutinins were present which differed from those of the mothers and indicated that a child may develop its own agglutinin during fetal life. Normal hemolysin for sheep corpuscles was transmitted from mother to fetus in only a few instances and whether the group of the child is the same or differs from that of the mother seemed to make no difference. Iso-hemolysin occurs in the blood of some new-born infants, and the resulting hindrance to agglutination may be avoided by inactivation of the serum which may even increase the agglutinative titer. Intoxications of pregnancy, birth difficulties or icterus neonatorum do not seem to be related to blood grouping.

FROM AUTHOR'S SUMMARY.

ISOHEMAGGLUTINATION IN MOTHERS AND NEW-BORN CHILDREN. P. MORVILLE, *Acta path. et microbiol. Scandinav.* **6**:39, 1929.

The isohemagglutinative groups were determined for 500 mothers and their 518 children, of whom 63.1 per cent belong to the same blood group as the mother,

and 61.2 per cent had iso-agglutinin present at birth. When mother and child belonged to the same group iso-agglutinin was more frequently found at birth, in 95 per cent when the group was O as contrasted with about 50 per cent when the group was A or B. When the group of the child differed from that of the mother iso-agglutinin was present in the child at birth only when one of them was in group O, and a child in group O with a mother in group A or B does not have the agglutinin combination  $a + b$ , but has only the agglutinin which is present in the mother. The conclusions from these studies of children at birth and at different ages are that iso-agglutinin passes from the mother's blood to the fetal blood in every instance but is often removed by the child's corpuscles, that the agglutinin present at birth is not the child's own, that the child's own agglutinin is in most cases developed at the end of four months but cannot always be expected in less than one year, and that the receptor (agglutininogen) is always present at birth though possibly weak and not easily determined. Certain paradoxical cases are described. Agglutinin and receptor are regarded as related properties due not to different, mutually independent heredity-factors, but to various hereditarily regulated stages of the same factor, and on the basis of this theory the group characteristics become an expression of genuine immunization. Experimental support is considered essential.

ETHEL B. PERRY.

### Tumors

LYMPHO-EPITHELIOMA. JAMES EWING, *Am. J. Path.* 5:99, 1929.

The present available data seem to call for the recognition of a particular form of epidermoid carcinoma occurring especially in the nasopharynx and designated by Regaud and Schmincke as lympho-epithelioma. The tumors arise from modified epithelium overlying lymphoid structures in the tonsils, the base of the tongue and the nasopharynx. They occur at all ages, frequently in young subjects, grow slowly, are often overlooked, tend to produce early metastases in the neck and later widespread extensions to the liver and bone marrow, and are generally fatal. They exhibit a marked primary response to radiation. The diagnosis must be based on the structure, which shows sheets of pale staining epithelial cells, often in syncytia, and infiltrated with many lymphocytes, both in the primary tumor and in metastases. The diagnosis may not be based on clinical appearances, course, location or radiosensitivity. Other tumors of the same regions are radiosensitive and produce early metastases to lymph nodes, bones and viscera. Anaplastic carcinomas may be distinguished by their more rapid course and cellular structure. The exact scope of lympho-epithelioma is not yet clear. Tumors of transitional epithelium located in many areas of the nasopharynx and lining the ducts of mucous glands seem to produce tumors showing many of the characteristics of lympho-epithelioma. It seems possible that the admixture of lymphocytes may be the result of a low grade inflammatory process occurring in certain other tumors, but their appearance in metastases is probably not to be explained in this way.

AUTHOR'S SUMMARY.

BIOPSY HISTOLOGY IN THE GRADING OF RECTAL CARCINOMA. FRED W. STEWART and JOHN W. SPIES, *Am. J. Path.* 5:109, 1929.

The histologic grading of rectal carcinomas in accordance with the suggestions of Rankin and Broders is of value in estimating the probable course of the disease. Small biopsy specimens are sufficient for such grading. Repeated biopsies do not show that change in type occurs sufficiently often during the course of the disease to interfere seriously with the prognosis suggested by the grade given at the time of the first biopsy.

AUTHORS' SUMMARY.

NEURO-EPITHELIOMA OF THE CEREBELLUM. PAUL C. BUCY and WENDELL S. MUNCIE, *Am. J. Path.* 5:157, 1929.

Neuro-epitheliomas are composed of primitive spongioblasts, and, as such, arise from the parent cells of ependymal tissue. Though more commonly arising from the ependyma of the spinal cord and from the retina, they may arise from ependyma elsewhere. A review of the literature shows that the case here reported is the fifth authentic case of neuro-epithelioma of the brain, and the second involving the cerebellum.

AUTHORS' SUMMARY.

SO-CALLED INFECTIOUS SARCOMA OF THE DOG IN AN UNUSUAL ANATOMIC SITUATION. WILLIAM H. FELDMAN, *Am. J. Path.* 5:183, 1929.

The more important literature pertaining to the transmissible lymphosarcoma of dogs is reviewed. A case is described in which two tumors, which morphologically were indistinguishable from transmissible sarcoma of the genitals, appeared respectively in the orbital space and under the skin of the frontal region of a young dog. The genitals were not affected. Although transplantation was not attempted, there seems sufficient histologic evidence to substantiate a diagnosis of transmissible lymphosarcoma. The word "transmissible" is preferable to the older term "infectious," since there is not evidence bacteriologically or otherwise that these growths are dependent for their origin on an infective factor in the accepted sense of the word. It could not be determined whether each growth had a spontaneous origin or whether one represented a metastasis from the other. The possibility of the tumors being the result of transplantations from a vaginal tumor of the mother at the time of birth was considered, but this was not subject to proof since the parentage of the puppy could not be traced.

AUTHOR'S SUMMARY.

THE REACTION OF THE SKIN TO OILS AND TARS. C. C. TWORT and J. M. TWORT, *J. Hyg.* 28:219, 1928.

A number of substances applied to the skin may cause a hyperplasia, which may recede when the irritant is removed or become the site of a malignant tumor. Acute hyperplasia is more liable to recede than chronic. Agents that produce acute hyperplasia differ in their ability to excite the formation of tumor. Agents can be concentrated so that weak tumor producers may become strong ones, these tumors rarely becoming malignant. The malignant possibilities of agents vary although all other qualities may be equal. The epithelial cells acquire a certain degree of tolerance for agents applied. They can be rendered hypersensitive to tar applications, however, by treating them originally with other agents.

H. E. LANDT.

TUMOR IMMUNITY. THOMAS LUMSDEN, *J. Path. & Bact.* 32:185, 1929.

The existence in the fresh serum of normal animals of nonspecific cytotoxins (heterotoxins) effective against the tumor and normal tissue cells of foreign animals is demonstrated. These cytotoxins are of the nature of labile immune bodies. They are ineffective in the absence of complement. The tumor and normal tissue cells of any particular species are specifically "protected" against damage by homologous cytotoxins, whether naturally existing or experimentally produced. The nature of this "protection" has been investigated and is described.

AUTHOR'S SUMMARY.

IMMUNE REACTIONS AND CANCER. F. C. PYBUS and H. R. WHITEHEAD, *J. Path. & Bact.* 32:195, 1929.

The serum of rabbits immunized against mouse carcinoma has a harmful effect on mouse carcinoma, heart and kidney cells growing in vitro. The effect on heart cells is slightly less pronounced than on carcinoma and kidney cells, but there is no marked specificity of the immune serum for carcinoma cells. The

serum of a rabbit immunized against human carcinoma still serves as a culture medium for mouse carcinoma, although it is not so good as normal rabbit serum. The growth of normal mouse tissues is also not so good in the immune serum. These experiments contribute no evidence, therefore, to prove the existence of antibodies common to the malignant cells of different animal species.

AUTHORS' SUMMARY.

EXPERIMENTAL CANCER AND HALOGEN SALTS OF MAGNESIUM. PIERRE DELBET, HENRI GODARD and C. PALIOS, *Bull. de l'Ass. franç. p. l'étude du cancer* **27:515**, 1928.

The experiments of Delbet and his associates were performed on guinea-pigs in whose gallbladder they inserted sterile gravel. The animals were divided into two groups one of which was treated with salts of magnesium and the other served as controls. The guinea-pigs were killed 24, 63, 72, 90 and 105 days after the operation. Those animals that have not received the salts developed marked cholecystitis with vesicular lesion which suggested a malignant disease. The animals treated with salts of magnesium showed no disease of the gallbladder.

B. M. FRIED.

THE ACTION OF HALOGEN SALTS OF MAGNESIUM ON THE EVOLUTION OF GRAFTED CANCER. PIERRE DELBET and C. PALIOSE, *Bull. de l'Ass. franç. p. l'étude du cancer* **27:525**, 1928.

In a previous note Delbet reported experiments on white mice to the effect that the growth of an epithelioma is considerably retarded when the rodent is treated with salts of magnesium and also that it is impossible to reinoculate a tumor which has grown in mice treated with this salt.

These experiments concern themselves with the effect of the salts of magnesium of the growth of a sarcoma and of three different types of epitheliomas. The "magnesiated" animals received bread soaked in the salt of magnesium and also subcutaneous injections of the salt which was composed of magnesium chlorate, magnesium bromide, magnesium iodide, 0.0002 Gm., and magnesium fluoride. The experiments have shown that the tumor progressed much slower in animals that received the drug than in the controls.

B. M. FRIED.

THE TREATMENT OF CANCER WITH COLLOIDAL LEAD. G. LOEWY and J. LOISELEUR, *Bull. de l'Ass. franç. p. l'études du cancer* **27:549**, 1928.

Borrel has produced evidences to show that glycogen has a particular affinity for the cancerous cells. Loewy and Loiseleur have succeeded in fixing colloidal lead on glycogen which they thought might serve as a vehicle to transport the metal toward the malignant cell. It is remarkable that the chemical thus prepared is supported in much higher doses than when administered without glycogen. It leads, however, to an anemia characterized by the usual signs and symptoms of plumbism. The glycogen-lead treatment was applied to different types of tumors (carcinoma of breast, osteogenetic sarcoma, melanotic sarcoma) without any appreciable results.

B. M. FRIED.

EMBRYONAL GRAFTS AND MALIGNANT TUMORS. N. PETROFF and N. KROTKINA, *Bull. de l'Ass. franç. p. l'étude du cancer* **27:566**, 1928.

The authors have performed experiments on white rats by injecting into these rodents embryonic pulp from rats varying from 1 to 3 cm. in length. This was combined with: (1) indol and injected into the peritoneum; (2) lactic acid and injected subcutaneously into the gluteal region; (3) arsenic and injected subcutaneously into the thigh.

The first series led to the development of insignificant wounds. In the second series they noted the appearance of firm nodules having a tendency toward absorption. Finally, of twenty-six rats of the third series, two animals developed malignant growths identified as sarcomas.

The article represents a review of previous works on the same subject and also a discussion on the mechanism of the "malignisation" of the animal injected with the embryonic pulp. The authors believe that in instances when the malignant disease follows immediately the injection of pulp it is due to transformation of the injected material into a malignant disease; in those cases when a disease occurs months after inoculation it is caused by the hosts' cells under the influence of the embryonic pulp.

B. M. FRIED.

THE RELATIONSHIP BETWEEN THE PERIPHERAL NERVES AND THE DEVELOPMENT OF CANCER. ITCHIKAWA (KOITCHI), Bull. de l'Ass. franç. p. l'étude du cancer **27:590**, 1928.

Itchikawa states that a proliferation of nerve fibers occurs in benign or malignant tumors whether spontaneous or experimental. He also noted that the pre-existing nerve fibers degenerate in neoplastic tissues. He thinks that the rôle of the nerves is most important in the development as well as in the regression of tumors.

B. M. FRIED.

LESIONS IN THE RABBIT'S EAR FROM PAINTING AND FRICTION WITH TAR. A. BABES and SERBANESCO, Bull. de l'Ass. franç. p. l'étude du cancer **27:597**, 1928.

The difference between the two procedures as seen in the early stages is as follows: When the tar is applied to the ear by friction, it induces a lesion akin to a senile keratosis which is regarded as a precancerous stage. Simple painting of the rabbit's ear with tar causes in the beginning a mere dyskeratosis (maladie de Darier) which as far as is known has nothing to do with a malignant disease. The authors maintain that the different results obtained are purely mechanical in origin.

B. M. FRIED.

THE APPEARANCE OF A CANCER THE THIRTEENTH DAY AFTER THE ONSET OF PAINTING WITH TAR. A. BABES, Bull. de l'Ass. franç. p. l'étude du cancer **27:605**, 1928.

In a few experiments with painting a rabbit's ear with tar, Babes obtained the appearance of an epithelioma within about two weeks after the first application of the irritant. In his opinion two factors are required for the appearance of tar cancer: (1) a chemical, and (2) a mechanical. The host himself, that is, the ear of the rabbit, and also the quality of the tar in all probability play a rôle in the precocious appearance of the malignant disease.

B. M. FRIED.

THE STRUCTURE OF THE CELLS IN UTERINE CARCINOMA. LAIMI LEIDENIUS, Arb. a. d. path. Inst. du Helsingfors. **5:334**, 1928.

This is an elaborate and thorough study of a large material the details of which are best studied in the original article. In all forms of uterine carcinoma, including cervical carcinoma treated with radium, the various structures of the cytoplasm of the normal epithelial cells are recognizable in the carcinoma cell; frequently, however, the characteristics are changed in some way or other.

CARCINOMA OF THECA INTERNA OF LUTEIN CYST. J. WALLART, Arch. f. Gynäk. **135:485**, 1929.

The growth occurred in a woman, aged 45, three years after giving birth to a healthy child.

## Technical

THE VALUE OF THE COSTA REACTION FOR THE DEMONSTRATION OF ACTIVE TUBERCULOSIS. M. TROJAN and F. PONGOR, *Ztschr. f. Tuberk.* **52**:209, 1928.

The mechanism of the reaction is still unknown. It is considered to be of definite value for the diagnosis of activity in tuberculosis. Although the reaction is nonspecific, it is independent of menstruation. The technic is simple and quick, and requires only three drops of blood. It is therefore of wide applicability even in private practice.

MAX PINNER.

DEMONSTRATION OF TUBERCLE BACILLI IN THE SPUTUM WITH THE DARK FIELD METHOD. S. VON STUBENRAUCH, *Ztschr. f. Tuberk.* **53**:122, 1929.

The demonstration of tubercle bacilli with the dark field method is easy, but no more specimens are found positive than with the usual methods.

MAX PINNER.

THE COSTA REACTION IN TUBERCULOSIS IN CHILDHOOD. K. NÜSSEL and H. HELBACH, *Ztschr. f. Tuberk.* **52**:301, 1928.

The reaction is less sensitive than the sedimentation reaction of erythrocytes, but it is recommended particularly for examination of children because it requires only a small amount of blood.

MAX PINNER.



# Society Transactions

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, April 8, 1929*

ESMOND R. LONG, *President, in the Chair*

### SPONTANEOUS CHRONIC GLOMERULONEPHRITIS IN A RAT. R. H. JAFFÉ.

The numerous fruitless attempts to produce experimentally a condition similar to the glomerulonephritis in man and the rareness of the spontaneous occurrence of such a condition in animals warrant the demonstration of the renal changes that were observed in an apparently normal rat. The rat was one of the controls used by Prof. W. C. Rose of the chemistry department of the University of Illinois in his studies on the effect of certain diets on the kidneys. It was under observation for two hundred and ninety-seven days and had received fully adequate food, permitting rapid growth. At the end of the experiment, the animal was killed, and since it was considered normal the urine was not examined. Except concerning the kidneys, autopsy did not yield any unusual observations. The weight of each kidney was 1.2 Gm. The weight of the heart was not taken. Examination of the blood revealed a marked increase of the nonprotein nitrogen, which was 101.4 mg. per hundred cubic centimeters as compared to 45 mg. for the normal rat.

The kidneys, which were mailed to me fixed with formaldehyde, were a light yellow-gray. The surface to which the capsule was adherent showed flat granular elevations just visible to the naked eye and separated by shallow depressions of a darker gray. On sections made by cutting, there was no difference in color between the cortex and the medulla, both being of the same pale yellowish-gray hue.

Under the microscope, there was great similarity to the histologic changes of chronic glomerulonephritis in man. This similarity involved the changes of the glomeruli and tubuli as well as those of the stroma and the blood vessels. In the glomeruli, various stages of hyaline obliteration were observed. There were large glomeruli with distended tufts which were filled with swollen and proliferated endothelial cells. The cytoplasm of these cells was filled with fat droplets. The epithelium of Bowman's capsule too, was found proliferated and, in places, was arranged in several layers. The capsular space was reduced to a narrow slit or had entirely disappeared. Other glomeruli showed a diffuse hyaline degeneration of the wall of the tufts, the tips of which fused with the thickened capsule. Single lipid-filled cells were embedded with the hyaline material. Finally, there were glomeruli completely transformed into a hyaline body.

Many of the convoluted tubuli were atrophic. The small epithelial cells were filled with single and double refractive fat droplets. The atrophic areas alternated with others in which the tubuli were wide and were lined by a flat epithelium. Their lumen contained a pale-stained homogeneous material. Here and there was a small cyst with a basophilic colloid-like content. The collecting tubuli of the medulla were dilated and filled with hyaline casts, which, in the sections stained with sudan III, took a pale yellowish-gray.

The stroma was increased especially about the atrophic tubuli. There were small perivascular accumulations of lymphocytes. The small arteries, in particular the interlobular branches stood out distinctly because of the thickness of the wall. The muscle fibers of the media were hypertrophic, and there was a thin layer of hyaline material between the endothelium and the internal elastic membrane. In places the entire wall was transformed into a hyaline material. In these places, fat stains revealed lipid deposits.

In its details as well as in the combination of these details the kidney of this rat was an exact duplicate of a human secondary contracted kidney. There was the hyaline obliteration of the glomeruli on an inflammatory basis, the complicating lipoid nephrosis and the arteriosclerosis. The change was entirely different from what frequently is described as an experimental nephritis and which is but the result of a severe degenerative process of the tubular epithelium, a chronic nephrosis. It is also different from the spontaneous renal lesions often encountered, especially in dogs and rabbits, which are interstitial inflammatory processes from ascending urinary infections or from metastatic embolic processes.



Spontaneous chronic glomerulonephritis in a rat. Note the various stages of hyaline obliteration of the glomeruli, the atrophic and distended tubuli contorti and the hyaline casts in the latter. There are two small cysts near the left edge. Stained with hematoxylin and eosin;  $\times 100$ .

#### DISCUSSION

H. G. WELLS: A number of the mice in Miss Slye's collection had glomerulonephritis associated with an enlarged heart and hydrothorax. Crescent-shaped hyperplasias of the cells lining Bowman's capsule were never observed.

THORACIC NEUROBLASTOMA. GEORGE RUKSTINAT and H. D. COUNTRYMAN.

A colored girl, aged 3 years, became unable to walk following intermittent attacks of "cold and fever" for four months. She had characteristic evidences of consolidation in the right lung and in addition accentuated right patellar and achilles

reflexes, right patellar and ankle clonus and a bilateral Babinski sign. X-ray plates disclosed a neoplasm in the right lung field extending across the midline downward to the level of the eighth rib peripherally and medially to the cardio-diaphragmatic angle. The essential items of the anatomic diagnosis were: primary mediastinal neurocytoma with hemorrhage; tumor erosion of the second and third thoracic vertebrae, and marked compression atelectasis of the right lung. The tumor, 13 by 10 by 6 cm., was attached to the apex of the right lung and right side of the mediastinum. Its rough fibrous capsule was from 1 to 2 mm. thick, dull gray and speckled occasionally with pin-point yellow dots of fat. The surface of the tumor, particularly posteriorly, was irregular from nodules from 1.5 to 4 cm. in diameter; about half of these were soft, the rest firm. On broad surfaces made by cutting, the upper one third of the mass consisted of firm grayish-pink tissue dotted irregularly, about 5 per cent by pin-point yellow specks. In some places this gray tissue was arranged in longitudinal and interlacing fine bundles; in others it formed compartments from 2 to 10 mm. in diameter, filled with friable yellow masses. The arrangement resembled most a sponge into the pores of which sawdust had been packed. Sections of the tumor were stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, sudan III and by the special methods of Weigert-Pal and Bielschowsky. The tumor capsule was heavily cellular with fibroblasts and, generally slightly infiltrated with small lymphocytes. Where it bordered on the spongy portions of the tumor it was invaded in irregular serrations by clumps of small round to oval cells only slightly larger than a small lymphocyte with a hyperchromatic nucleus and a peripheral rim of cytoplasm only about one-fifteenth the diameter of the nucleus. Occasionally, these cells were in cords from five to six cells wide, but more often they appeared in medullary masses. Occasionally, there were annular arrangements of these cells and from seven to twelve encircled a finely speckled mass. These were regarded as rosetts. More centrally in the tumor the small cells gave way to a delicately fibrillar structure enclosing purple hyperchromatic masses in places of which were hints of necrotic cell bodies. These masses represented the yellow flecks noted grossly. With Weigert-Pal stains huge tangles of neurofibrils appeared between the small type of cells and definite processes were discernible on large ganglion cells which occurred in definite clumps near the softer parts of the tumor. Masses of neuroblasts were evident in the peribronchial lymphatics. The tumor herein reported was believed to be uncommon and represented a combination of a ganglioneuroma and a neuroblastoma.

#### DISCUSSION

PERCIVAL BAILEY: Three distinct types of sympathetic tumors may be distinguished, usually called chromaffin tumors, ganglioneuroma and neuroblastoma. I object to the last term. The implication is that the neoplastic cells are neuroblasts. This implication is based largely on negative evidence; the fibrillary material does not stain with aniline-blue nor with phosphotungstic acid hematoxylin; being neither collagen nor neuroglia it must be nervous fibers. The conclusion does not follow even though aniline-blue stained all the mesodermal fibrillae and hematoxylin all the neuroglia. The only positive evidence is based on the results of Bielschowsky's method, which is notoriously unspecific. Herxheimer's illustrations show fibrils which are much more characteristic of reticulin than of nervous fibers. The structure of the more differentiated tumors, the ganglioneuromas, shows that the neoplastic cells are multipotential and may form nervous cells, neurinomatous cells or chromaffin cells. It seems better to employ a noncommittal term such as sympathicoblastoma for the undifferentiated tumors.

H. G. WELLS: I have recently seen a mediastinal tumor in a child, producing pressure on the right side of the trachea. Histologically, it is a ganglion cell tumor.

#### HEMANGIOMA OF BONE. PAUL C. BUCY.

A pathologic study of seven cases of hemangioma of the bone and a review of the literature were presented. Hemangioma of the bone is a rare clinical

entity; only thirty-nine clinical cases are known. Of these, thirteen were located in the skull, twelve in the vertebrae and the remaining fourteen in various other bones of the body. Pathologically, hemangioma of the vertebrae is common, having been demonstrated by Töpfer in more than 11 per cent of all bodies examined. However, these growths rarely produce symptoms. Hemangioma of the bone is more prevalent in females than in males at a ratio of about 55:45, and is more commonly found during the fourth and fifth decades. Multiple lesions involving other bones or soft tissues are frequent.

The material presented confirmed Hitzrot's statement that hemangiomas of the long bones occur near the epiphyseal line. Grossly, the lesions presented a swelling of the involved bone covered by intact periosteum. The tumors were of bony hardness and on section were seen to be traversed by numerous bony trabeculae between which the vascular tissue could be seen. Cystic forms have been reported. Microscopically, the series included six cavernous hemangiomas and a capillary hemangioma of the ulna. The difference was only one of size of the vascular channels. In the cavernous hemangiomas the channels were very large, while the spaces in the capillary hemangiomas were but little larger than capillaries. Practically no endothelial proliferation was seen. The amount of intervascular connective tissue varied greatly in different cases.

Study of the spicules of bone revealed two types of changes, formative and destructive. The former were characterized by the formation of new bone by osteoblasts which could be seen as a single layer of cells along the spicules of bone, and by the ossification of fibrocartilage which was particularly interesting on the surface of the laminae in the case of hemangioma of the vertebrae. Destructive changes were seen in the numerous necrotic pieces of bone present and in the erosion of the bone by numerous multinucleated giant cell osteoclasts.

Several lantern slides illustrating the various histologic characteristics were shown.

The complete report is published in *Am. J. Path.* 5:381 (July) 1929.

#### CELLULAR CHANGES OF THE ARACHNOID IN LEPTOMENINGITIS. THEODORE T. STONE.

Eleven cases of leptomeningitis were studied: three meningococcic, six tuberculous and two syphilitic. In the epidemic meningococcic and purulent types, study of the arachnoid revealed the presence of large, circular or oval cells which appeared attached to the inner surface of the arachnoid membrane. These cells contained an eccentrically placed nucleus with cytoplasm-containing substances that stained black with osmic acid and in many instances contained structures resembling cocci. In other parts of sections in these types evidence of arachnoid cluster formation could be made out. Many parts of the arachnoid were devoid of cells. In the latter instances, the subarachnoid space contained large cells with eccentric nuclei and reticulated cytoplasm. The latter was made up of inert bodies, fat globules, organisms and blood cells.

In tuberculous and syphilitic leptomeningitis no such relationship existed between the arachnoid membrane and the subarachnoid space. In early acute cases of leptomeningitis in man, the cells lining the arachnoid and trabeculae may become macrophages.

#### RETROPERITONEAL CYSTS. W. H. DROEGEMUELLER, JR.

The first reported case of a retroperitoneal cyst was probably that described by the Florentine anatomist, Benivieni, in 1507 (*De abditis nonnullis ac merandis moborum, et sanationum cousis*, Florence, 1507). The first comprehensive résumé of the subject was published by Hahn in 1887 (*Berl. klin. Wchnschr.*, 1887, p. 408). Five years later Braquehay (Arch. gén. de méd., 1892, vol 2) divided the history of retroperitoneal cysts into three periods: (1) the "anatomical period" from the time of Benivieni to 1850; (2) the period of "surgical interference on mistaken diagnosis" from 1850 to 1880, and (3) the "clinical surgical period" after 1880. In 1900, Dowd (*Ann. Surg.* 32:515, 1900) pointed out the embryonal origin of

many of these cysts. In 1907, just four hundred years after Benivieni's report, Niosi (*Virchows Arch. f. path. Anat.* **190**:217, 1907) collected 184 cases from the literature and classified them into: (1) cysts of intestinal origin; (2) mesenteric dermoid cysts; (3) cysts derived from the remains of the urogenital tract, and (4) a miscellaneous group of these cysts that did not belong to the three types differentiated by him.

The most satisfactory classification of retroperitoneal cysts thus far presented is that of R. M. Handfield-Jones (*Brit. J. Surg.* **12**:119, 1924), which is as follows: cysts arising from cell inclusions such as dermoid cysts; parasitic cysts; traumatic blood cysts; cysts developing in fully formed organs, as the retention cysts of the kidney and pancreas; lymphatic cysts, and cysts of urogenital origin.

To this list is added a further group differentiated by A. Stoney (*Brit. J. Surg.* **12**:789, 1925); namely, cysts associated with the mesocolon, which are apparently retroperitoneal in position.

Retroperitoneal parasitic, blood and dermoid cysts and cysts attached to adult organs, each have outstanding characteristics that make their classification certain. The differentiation of cysts of urogenital, lymphatic and mesocolic origin, however, is a much more difficult problem, for grossly, and in many respects microscopically, these cysts have essentially the same characteristics.

Lymphatic cysts are of comparatively small size and are of two types: chylous and serous. The former is recognized by the character of its contents and develops in the lymphatics which receive lymph from the intestines. The serous lymphatic cysts that are small are probably derived from simple dilatation of the lymphatics. It has been suggested that the larger cysts arise from anomalies in the primitive retroperitoneal lymph sac.

The pronephros, mesonephros and metanephros form the embryonic urogenital system, which undergoes a series of complex changes in growth and regression in the retroperitoneal tissues. In the development of the urogenital system there is opportunity for delay or failure in the normal degeneration of some tubular structure which may thus be a source of cyst formation. The tubules of the mesonephros have been observed long after they normally degenerate. These urogenital cysts have a dense fibrous wall, are usually monolocular, contain a clear serous fluid and are lined with a low columnar epithelium.

Mesocolic cysts may develop either in the mesocolon or between the mesocolon and the posterior celomic wall.

Following the elongation and contra-clockwise rotation of the developing gastrointestinal tract in early fetal life, the peritoneum covering the posterior abdominal wall and the mesocolon normally blend. When fusion is imperfect the large intestine becomes provided with a mesentery; when fusion occurs at the periphery but not over the whole surface, small spaces are left in which fluid may accumulate to form cysts. Such a cyst would be situated anterior to the retroperitoneal structures and have a lining of mesothelium.

The other type of cyst that develops within the mesocolon, according to the classification of some authors is a true mesenteric cyst, that is, one definitely located within the mesentery. These cysts arise from embryonic intestinal diverticula that have been observed in the development of the embryo. Their walls are lined with a columnar epithelium similar to that lining the intestine and are composed of fibrous tissue and smooth muscle.

The case here reported is that of a man, aged 70, who entered the Alexian Brothers Hospital on Feb. 17, 1929. The patient was in a stuporous condition and a satisfactory history was not obtainable. When awake he held his hand on the left side of his abdomen, suggesting some discomfort in that region. The patient's daughter said that for many years he had had a palpable mass in the lower part of the left side of the abdomen. This mass is said to have increased markedly in size during the last forty-eight hours of life. Cystoscopic examination revealed a normal bladder. The patient died on Feb. 20, 1929.

The postmortem examination by Dr. J. P. Simonds revealed the following conditions: arteriosclerosis of the coronary arteries with calcification; chronic myocardial fibrosis; brown atrophy of the heart; atheromatous changes in the mitral and aortic valves; hydropericardium; atheroma of the aorta; primary carcinoma of the bronchus to the left upper lobe with invasion and occlusion of the pulmonary artery to that lobe; gangrene of the upper lobe and of the upper part of the lower lobe of the left lung; healed, calcified tuberculosis of the right lung; chronic fibrous pleurisy, obliterative on the left side; chronic perihepatitis; perisplenitis cartilaginea; chronic pancreatitis; arteriosclerotic contractions of the kidneys; multiple retention cysts of the right kidney, and large left retroperitoneal cyst.

This cyst was in the left side of the abdominal cavity, was ovoid, contained 2 liters of clear yellowish fluid and measured 30 cm. in length by 22 cm. in diameter. The transverse colon passed along its upper surface, and the splenic flexure lay behind its upper end. The descending colon, which was empty, passed downward along the lateral surface for about three fourths of the length of the cyst, then passed over the cyst to the right, thence down and back to a position immediately beneath the inferior surface of the cyst. The root of the mesentery and the duodenum was pushed to the right; the spleen lay behind and to the left, and the stomach rested on the upper surface of the cyst. The left kidney lay well above and slightly behind the cyst and the left ureter passed down the posterior and lateral surface of the cyst to which it was adherent. The aorta was also adherent to it and pushed to the right.

Five centimeters from the upper end of the cyst was a constriction. Above this constriction the cyst bulged slightly and then tapered to a thin-walled tube, 6 cm. in length, which turned downward under the main cyst. This tubular prolongation varied between from 3 to 10 mm. in diameter, and lay along the left half of the front of the second and third lumbar vertebrae. Extending from the apex of the cyst downward along the posterior surface of the large cyst was a firm yellowish-red translucent and tortuous cordlike structure from about 1 to 2 mm. in diameter, resembling a dilated lymphatic, and ended below in a somewhat purplish trilobed mass, each lobe measuring approximately 7 mm. in diameter and 5 mm. in thickness. When this cordlike structure and the trilobed mass were incised after fixation in formaldehyde, they were found to be filled with a firmly coagulated translucent orange colored material.

The lining of the tubular prolongation of the main cyst was smooth and consisted of an incomplete single layer of flat cells; that of the cyst itself was roughened by calcified masses and no definite layer of lining cells was found. Microscopically, the wall of the cyst was composed of a dense fibrous tissue.

The specific gravity of the fluid was 1.024. It coagulated on standing and became dark brown. Examination of the sediment centrifugated from 50 cc. of the fluid showed a few red blood corpuscles and leukocytes.

The cyst was probably of embryonic origin. Its general relations did not seem to correspond with the urogenital type. If the cyst arose from a mesonephric tubule, one would expect it to lie posterior to the ureter and to be lined with cuboidal epithelium. That this cyst belonged to the lymphatic type cannot be definitely excluded. If it arose from the portion of the retroperitoneal lymph sac which is median in position, one would not expect to find the relations of the cyst as they were; the ureter would be anterior to the cyst.

The structure, and especially the relations of this cyst, did correspond with the mesocolic type. From its position, lying at first medial and then posterior to the descending colon, inferior to the transverse colon, superior to the sigmoid and anterior to the ureter, it seemed reasonable to assume that this cyst developed in a sac formed by the incomplete fusion of the mesocolon and the posterior abdominal wall. Hence, I found a thick fibrous wall and a lining of mesothelium which had been partly destroyed by the marked calcification of its inner surface.

## NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, April 11, 1929*HARRISON S. MARTLAND, M.D., *in the Chair*

## THE SIGNIFICANCE OF HISTOLOGIC EXAMINATION OF THE SKIN IN CLINICAL DIAGNOSIS. WALTER J. HIGHMAN.

General pathologists can scarcely realize how much has been written on pathologic conditions of the skin. There have been about twenty outstanding skin pathologists throughout the world, with perhaps an equal number now coming forward, but a bulky literature attests the fact that more has been written on the subject than the few competent authors could possibly have produced. In almost every dermatologic publication an undue amount of space is devoted to histologic description, and if these descriptions were shuffled and redistributed at random no one would be the wiser, for most of them are vague and unconvincing. With little talent for portrayal, unshaded references to round cells, plasma cells, perivascular infiltration and other stock phrases are employed, with the net result of nothing distinctive in the description.

The habit has been formed of calling such a description a histologic diagnosis, and the clinician entertains a feeling of outrage if microscopic study does not furnish him the desired diagnosis, or if the observations are not in accord with his hopes. To appreciate the situation, a nondermatologist must be reminded that there are more than 500 so-called skin diseases of which the inflammations are usually not distinctive as to microscopic appearance. This fact is the essential one to be considered.

For a moment, however, a short digression will narrow the issue. Tumors of the skin are distinctive enough histologically. In fact, the clinical identification of neoplasms falls so far short of the microscopic identification that the latter becomes an imperative aid in the diagnosis of tumor and in the recognition of the subtler types of nevi, or better, embryonal anomalies. All the connective tissue and most of the epithelial neoplasms, both benign and malignant, including such lesions as molluscum contagiosum, pointed condylomas and the like, possess characteristic minute structure. The majority of regressive changes, including dystrophies, like the sclerodermas, atrophies, colloid alteration and calcification of the skin, are individual under the microscope as are also many of the infections, provided the specific parasite can be demonstrated; however, on mere anatomic grounds, this is by no means so. But in noninfectious inflammations of the skin and in some other types of lesions, fundamental difficulties requiring explanation arise, which render the microscope scarcely serviceable in diagnosis.

Inflammatory dermatoses are numerous, and dermatologists have differentiated them from one another with astute overrefinement, their concepts having been descriptively formed with scant reference to etiology. What little is known of the causes of skin diseases indicates strikingly that eruptions due to a single agent may vary widely in appearance and, conversely, that unrelated agents may produce identical dermatoses. An example of the first would be the various iodide lesions; of the second, the toxic erythema or the wheal. Thus, the very foundation of descriptive dermatology is faulty. Moreover, these facts are reflected in the histology of inflammations of the skin. The elements composing microscopic architecture are few, and the range of their combinations is not wide. But the principles governing macroscopic pathology of the skin, which is what clinical dermatology is, have also governed its microscopic pathology, and keen attention has been given to the most trifling minute changes, in the hope that clinical limitations would be thus supplemented. In the main the effort has been a failure, and as far as inflammatory dermatoses are concerned, it seems that microscopic pathology offers little aid in diagnosis. Moreover, to talk of histologic diagnosis in this connection is unphilosophic.

A few inflammations have an almost uniformly characteristic aspect, if not a pathognomonic one. When mast cells are abundant, lichen planus and urticaria pigmentosa are such. Psoriasis, parapsoriasis, lupus erythematosus, eczema and some forms of lichenification are often distinctive enough to be recognized for what they are, under the microscope. Their identification, however, rests on such meticulous details that there is no opportunity in a paper of this sort to do more than state the fact. More often, an arbitrary construction of the slides is unjustified. The erythemas, urticaria, pemphigus and related diseases, the general scaling eruptions known as exfoliative dermatitides, ichthyosis, and another score or so of inflammations, subject to their stage, all present the appearance of acute, subacute or chronic exudative inflammation or productive inflammation, as the case may be, with certain more or less dominant features in the epidermis or cutis vera or individual elements of these which might correctly guide an experienced dermatopathologist to venture an opinion as to the clinical nature of the lesion, but certainly no diagnosis.

Cutaneous syphilis, lepra, rhinoscleroma and tuberculosis in its multifarious aspects are often distinguishable from one another and from similar lesions caused by various fungi. But the most seasoned microscopist would not have the hardihood to be arbitrary in borderline cases. In lepra the lepra cells and in rhinoscleroma the rhinoscleroma cells and Russell bodies may furnish a clue, but not invariably. Other features would provide further tentative guides. Here, again, circumspection would necessarily be desirable, except when the parasite can be found; but this is scarcely a fair criterion under the conditions discussed in this paper, for the parasite might more easily be demonstrated outside the section.

The so-called lymphodermas, that is, infiltrations of the skin in leukemia, Hodgkin's disease and mycosis fungoides, are often typical enough to be identified by a shrewd observer. More frequently, though, this is not so; nor can the prodromal phases of these conditions be recognized with any certainty. Of the eruptive fevers, measles, scarlatina and the related erythemas are not distinctive; smallpox and chickenpox, and in this connection zoster are, within limits, distinctive. Certainly, however, to characterize this as diagnosis would be an exaggeration.

Thus histologic study of the skin is a first-rate diagnostic aid only for neoplasms. It is a fair diagnostic guide in granulomatous infections and in lymphatic infiltrations. In some of the dystrophies, it can also be so regarded. In inflammations only the microscopic appearance of lichen planus and urticaria pigmentosa is distinctive, but these conditions are clinically so obvious that their microscopic distinctiveness is of no practical importance. In all other inflammatory processes, although the microscopic structure is often suggestive, no justification exists for talking of such a thing as microscopic diagnosis. Therefore, cutaneous histologic study, aside from its bearing on neoplasms, is of no great value in clinical diagnosis.

But to drop the matter here is hardly fair, either. Pragmatic ends are not the only ones to be served in science. Two points must be discussed. First, clinical dermatology is enhanced by a grasp of the minute architecture of lesions of the skin, if not from the diagnostic, at least from the intellectual, side. Since the histology of lesions of the skin has been so emphasized in the literature, a clinician not conversant with its broader meaning, at least to the extent of understanding what a histologic description purports to convey, is handicapped, partly through illiteracy and partly because he may be misled by inadequately trained writers. Second, cutaneous microscopic changes constitute a highly specialized field with which the general pathologist is not necessarily conversant unless he has troubled himself to master its minutiae, in terms of clinical dermatology. He must be a reasonably good dermatologist to be a reasonably accurate interpreter of microscopic changes in lesions of the skin. Any general pathologist can easily so equip himself, but few do. Dermatology is, after all, not the black art. On the other hand, few dermatopathologists have concerned themselves sufficiently with general pathology. What is necessary is that the dermatologist, dermatopathologist and general pathologist should endeavor to understand one another. Each of the three must include in his intellectual equipment much possessed by the



other two. In this manner, and subject to its inherent limitations, the study of microscopic changes in the skin may prove to be of greater value than it has hitherto in clinical diagnosis.

#### DISCUSSION

ALFRED PLAUT: The diagnosis of infectious diseases by means of histologic study of the skin is a field in which something practical can be done. When a patient has fever and a rash, and the differential diagnosis lies between typhus and typhoid fever, one is able within twenty-four hours to make a differential diagnosis by the excision of the areola. This was done in 1913 and 1914 by Eugen Fraenkel in Hamburg, and I had an opportunity to help in part of the work. The excision is quickly done; when the patient is drowsy, one does not need any preparation. With a sharp, curved pair of scissors the excision is made; two Michel clamps are applied, and the wound heals without further treatment. The lesion of typhus is so characteristic that it is really sufficient for diagnosis. On the other hand, the typical roseola of typhoid fever is not so characteristic. But a simple trick can help in the diagnosis here. One puts the excised roseola into broth in the incubator for ten hours; then one fixes, hardens and cuts the specimen. The bacilli multiply, and large heaps of bacilli can be easily seen in the stained slide. In a number of other infectious diseases, valuable information can be obtained from excision of the skin. One of my patients with miliary tuberculosis showed many small nodules in the skin, but in one instance they proved to be an intradermal accumulation of cocci, and thus had nothing to do with the tuberculosis. One patient who died of meningitis due to Friedländer's bacillus had a peculiar hemorrhagic lesion of the skin, and it was possible to demonstrate Friedländer's bacillus in the lesion. But here one has to be careful. The fact that an organism can be demonstrated in the lesion on the skin does not necessarily mean that the lesion is due to an organism. When a boy with epidemic meningitis has a large area affected by herpes on the hand and a coccus is recovered from it, no one would think that the herpes was due to the meningococcus; it was only there by chance. A lesion on the skin seen under the microscope showed some similarity to the lesion in typhus; it was present in a case of meningitis, and clinically looked like the lesion of erythema nodosum. In two patients with doubtful clinical pictures similar to those of typhoid fever, lesions on the skin were present. One patient turned out to have typhoid fever, but the skin lesion was not quite typical. Certainly a patient with an infectious disease may have another skin lesion at the same time. In spite of such exceptions, I think that it may be really of value, especially when there is danger of an epidemic or when a ship comes from a country which is infested with typhus fever, to make excisions of the skin. The pieces can be embedded in paraffin, and all tests made within twenty-four hours.

J. J. ELLER: I should like to add one point in regard to ulcerations of the mouth and penis. Clinical diagnosis is difficult in only a few cases of ulcers of these areas. In the mouth a chronic ulcer may be due to tuberculosis, syphilis or carcinoma, and the only way in which one can make a reasonably positive diagnosis is by studying sections microscopically. A section should be taken close to the border, because if it is not, one may make an incorrect pathologic diagnosis of granulation tissue, which means nothing; the same thing applies to ulcers of the penis. Chronic penile ulcers may be due to syphilis, tuberculosis, carcinoma or granuloma inguinale. It is important here, also, to take the section along with what is apparently a small piece of healthy tissue in order to have a fair chance of getting a correct diagnosis by microscopic study.

PAUL KLEMPERER: It might be interesting to mention a case of mild typhus known as Brill's disease, in which I found the characteristic lesions of typhus.

HARRISON S. MARTLAND: What impresses me most about Dr. Highman's paper is that as a dermatologist, he frankly admits that there are any number of skin diseases that cannot be distinguished from one another by histologic sections alone. He has not once spoken of the ubiquitous plasma cell. This is indeed an advance.

WALTER J. HIGHMAN: I do not know anything about the lesion of typhoid fever examined under the microscope; I have never seen it.

I appreciate what Dr. Eller said, but I mentioned that diagnosis of tumor is the one instance in which one is more certain of the diagnosis under the microscope than clinically, and I did not think that the details concerning tumors or the aforementioned plasma cells, which have been so widely press-agented, would be interesting.

#### A DIFFERENTIAL SILVER STAIN. GEORGE F. LAIDLAW.

Slides were exhibited showing that in normal skin fixed in Bouin's fluid (glacial acetic acid, 20; solution of formaldehyde, 100; saturated solution of picric acid, 300), the stain differentiates the epithelial cells from the cells of mesodermic origin. Surface epithelia and the epithelia of the hair follicles and of the sebaceous and sweat glands are silver positive. Fibroblasts, smooth muscle cells and the endothelia lining the vessels are invisible; they are silver negative. Collagen is purple or red; the argyrophil reticula remain outlined in black.

Tumor cells retain the silver-positive or silver-negative features of the cells from which they spring. In papilloma, adenoma and epithelioma, the epithelial cells are positive; the fixed mesodermal cells of the interstitial tissue are silver negative. In fibroma, lipoma, angioma and myoma, all cells are negative.

Sarcoma presents a further differentiation which agrees with Ménétrier's classification of sarcomas as sarcoma of the structural tissues and sarcoma of the blood-forming organs. The cells of the structural tissues, fibrous tissue, bone, smooth muscle and vessel endothelia are silver negative; fibrosarcoma, angiosarcoma and osteogenic sarcoma are silver negative also. In the blood-forming tissues, the bone marrow, the spleen and the lymphatic tissue, the parenchyma cells are silver positive; and the tumors arising from them are silver positive also. The cells of metastases retain the features of the primary growth.

Tissue fixed in solution of formaldehyde presents this differentiation, but not so constantly. There is a curious and constant difference between the two fixatives. In epithelia fixed in Bouin's fluid, the cytoplasm stains but the nuclei remain colorless; in cells fixed in solution of formaldehyde, the nucleus takes the stain but the cytoplasm is colorless.

#### TECHNIC

1. Fix the sections in Bouin's fluid for three days.
2. Embed in paraffin or celloidin, or make frozen sections.
3. Stick paraffin sections on the slide with Masson's gelatin glue and harden in hot solution of formaldehyde fumes; otherwise, they float off in the hot alkaline silver.
4. After removal of the paraffin, wash in running water for twenty minutes to remove the picric acid.
5. Mordant with the Mallory bleach: (a) 1 per cent tincture of iodine, three minutes; rinse in tap water; (b) 5 per cent sodium hyposulphite, three minutes; rinse in tap water; (c) 0.25 per cent potassium permanganate, three minutes; rinse in tap water; (d) 5 per cent oxalic acid, three minutes; wash well in running water for ten minutes.
6. Immerse in distilled water; change three times within five or ten minutes to insure clean slides entering the silver solution.
7. Del Rio-Hortega's lithium silver augmented to 10 per cent.  
Heat the stock solution in the oven to 50 C. and stain in the oven for five minutes. As an economic measure, the same silver solution may be used many times, being filtered before use.
8. Rinse with distilled water.
9. Solution of formaldehyde, 1 per cent; flood the slides several times for five minutes.
10. Rinse with distilled water.

11. Immerse in yellow gold chloride, 1:500, at room temperature for ten minutes; the gold solution may be used many times until it becomes pale.
12. Rinse with distilled water.
13. Pour oxalic acid, 5 per cent, on slide and leave for ten minutes.
14. Rinse with distilled water.
15. Pour sodium hyposulphite, 5 per cent, on slide and change as often as it becomes turbid for ten minutes.
16. Wash well in running water for ten minutes. Counterstain if desired and mount in balsam.

*Masson's Gelatin Gluc.*—Dissolve a bit of sheet gelatin 0.5 cm. square in 20 cc. of distilled water, warming over the flame. Place a row of clean slides on the warm plate at 45 C. Filter a large drop of gelatin solution on each slide and float the section on it. When the section spreads, stand the slide upright to drain, blot with absorbent paper and place immediately in the 45 C. or 50 C. oven, leaving an open dish of solution of formaldehyde in the oven. In thirty minutes, the sections are ready for staining with hematoxylin or the aniline dyes; for silver staining, it is better to leave the sections in the hot solution of formaldehyde vapor for several hours or overnight.

*Ten Per Cent Lithium Silver (Modified Hortege).*—To make 120 cc. in a 250 cc. glass stoppered graduate, dissolve 12 Gm. of silver nitrate, chemically pure, in 30 cc. of distilled water. Add 220 cc. of saturated solution of lithium carbonate, chemically pure, in distilled water. Shake well; let settle to about 70 cc. of precipitate; wash well with distilled water three or four times. After it has settled to about 70 cc. of precipitate, decant the wash water and add aqua ammoniac fortior, shaking constantly until the fluid is almost clear. Add distilled water to 120 cc., shake and filter into a brown glass-stoppered stock bottle. The solution keeps for many months; it is so strong that a slight precipitate of silver is negligible. Ordinary filter paper is apt to turn brown and discolor the solution while filtering. Use Whatman filter paper no. 40 or 42 or Schleicher and Schüll, no. 589.

This technic is a modification of Del Rio-Hortega's connective tissue stain, which has been popularized in this country by Foot. The writer's modifications are the increase of the silver to 10 per cent; the use of the Mallory bleach as a mordant for silver on tissue fixed in Bouin's fluid, and the intercalation of oxalic acid between the gold and the sodium hyposulphite. A more detailed account of the technic appears in the *American Journal of Pathology* for May.

#### DISCUSSION

ALFRED PLAUT: How does the nevus cell act?

GEORGE F. LAIDLAW: Silver differentiates two kinds of nevus cells which, in a general way, agree with Masson's hypothesis of a double origin, the one from the Schwann cells and the other from the epithelium. As Masson pointed out, the common nevus cells occur in the form of clusters and nucleated bands enclosed in a thin sheath of collagen. These cells are silver negative like the Schwann cells from which they are supposed to be derived. In the upper part of many nevi are found larger cells resembling epithelia or spindle and stellate forms like chromatophores; these cells are supposed to spring from the epithelium and, like the epithelia, they are silver positive. Further than this, I have not gone.

PAUL KLEMPERER: I wish to express my admiration for this work, because I feel that it is full of possibilities for the pathologist. If it actually works and, knowing Dr. Laidlaw, I have no doubt that it will, it will give us an opportunity to decide several morphologic questions which so far it has not been possible to settle. For instance, the origin of the small thymic cells can be decided, whether mesenchymal or epithelial in nature. It will be possible to decide whether the so-called alveolar epithelium of the lung is actually epithelial or mesenchymal in nature. I think that the work is of the greatest importance and that it should

be taken up at once in the laboratories. There is one question I should like to ask. Among the skin sections, I missed a tumor which is one of those that has given rise to much discussion: the so-called endothelioma. I am sure that Dr. Laidlaw has had the opportunity to see a tumor of this type, and I would be interested to know whether this method confirms the belief held today that the so-called endotheliomas of the skin are epithelial in origin. I would like to ask about the behavior of the reticulum cell; is it positive to silver?

H. S. MARTLAND: I feel the same as Dr. Klemperer does about Dr. Laidlaw's painstaking work. Are the histiocytes of the reticulo-endothelial system positive?

GEORGE F. LAIDLAW: I am not ready to say much about endothelioma. It is a debatable subject requiring much more study and material. I have not had the opportunity to stain an endothelioma of the skin.

H. S. MARTLAND: What about the Dorothy Reed cell in Hodgkin's disease? Is it positive?

GEORGE F. LAIDLAW: Yes.

WALTER J. HIGHMAN: Have you made any comparative studies with mycosis fungoides?

GEORGE F. LAIDLAW: No.

PAUL KLEMPERER: Is it possible to use this stain with old material which has been fixed in solution of formaldehyde?

GEORGE F. LAIDLAW: Yes.

#### MULTICENTRIC BASAL CELL EPITHELIOMA: A POSSIBLE CLINICAL ENTITY. PAUL GROSS (by invitation).

After a brief reference to the literature, especially the work of Jadassohn and Graham Little, Henry Janeway's article on the early stages of epithelioma was mentioned as the first which associated the clinical picture of superficial basal cell epithelioma with the histologic picture of multicentric basal cell proliferation.

A short summary was given of the essential clinical features of this condition, which so frequently resembles some other superficial dermatosis. For the proper conception of histologic peculiarities, the author considered the long duration of the lesions of importance.

The trunk is the favorite location. Multiplicity is not an essential requirement for diagnosis. The clinical resemblance to Bowen's precancerous dermatosis is mentioned.

With the aid of lantern slides of sections from three patients observed by the author during the last three years, the histology was described and discussed.

The characteristics are found in multicentric epithelial budding, which is made up of undifferentiated basal cells and is usually derived and in continuity with the basal cell layer of epidermis, but in one slide an identical proliferation was demonstrated from the lower portion of a follicle.

The author was greatly interested in the frequent occurrence of slits and large spaces which surround these basal cell proliferations and are lined by dense connective tissue; but he did not feel justified in following Lipschutz, who interpreted them as preformed lymphangiectatic spaces.

Infiltration in the cutis with lymphocytes and plasma cells was found in all sections. Finally a slide was demonstrated, showing the transformation of a multicentric epithelioma into a typical reticular basal cell cancer.

In discussing the histologic observations and the interpretation by different authors, the author felt that a certain relationship, even histologically, seemed to exist to Bowen's precancerous dermatosis. The question arises as to whether both conditions are precancerous or true intra-epidermal cancers, and in both a nevus preformation seems to be probable.

PULMONARY STENOSIS IN AN ADULT WITH BACTERIAL ENDOCARDITIS. LOUIS FAUGERES BISHOP, LOUIS FAUGERES BISHOP, JR., and S. G. WALLACE (by invitation).

*History.*—A woman, aged 32, was seen first on March 12, 1925. She stated that she had always suffered from dyspnea on exertion which for the past year had increased in severity. She also suffered from asthenia and insomnia.

She gave a history of measles, mumps, chickenpox, pneumonia and severe scarlet fever in childhood. She was reported to have had heart trouble at 1 year of age. At 14 years of age she had "rheumatism." She had a chronic cough, but no expectoration or hemoptysis. Her appetite had always been poor. The menstrual history was irregular. Her marital history disclosed one normal pregnancy; her husband died of tuberculosis.

*Physical Examination.*—The patient, a blond, was thin and pale. The veins of the neck were distended. The heart was moderately enlarged; the apex was visible outside the nipple line, with marked visible apical pulsation and definite thrill over the mitral area. The cardiac rhythm was regular; the rate was 92. A loud, blowing systolic murmur was heard over the entire precordium, most marked over the pulmonic area, transmitted to the left, and an occasional pre-systolic murmur was heard over the mitral area. The blood pressure was systolic 110, diastolic 70. The liver was palpable 2 fingerbreadths below the costal margin.

The blood count showed 6,300,000 red blood cells; hemoglobin, 70 per cent; white blood cells, 8,000. The blood chemistry was normal. The Wassermann test of the blood was negative. The urine showed nothing.

The electrocardiogram showed a normal sinus rhythm; normal conduction time, and a marked right ventricular preponderance; the P wave was abnormally large; there was an inverted T wave in leads II and III.

*Course.*—In 1927 the patient went to California and led a restful, outdoor life, but her cardiac reserve decreased. She returned in February, 1928, with increased dyspnea, rapid pulse, nervousness and a hacking cough. Examination in March, 1928, showed that the spleen and liver were palpable, and they became enlarged progressively in spite of continued rest at resorts. In September, 1928, she returned to New York. On examination, the mucous membranes were pale; petechiae were present in the right conjunctiva; the spleen was palpable almost to the umbilicus, and was hard and firm; the liver was palpable 2 fingerbreadths below the costal border. The cardiac examination showed no change. The temperature ranged between 100 and 104 F. A blood count showed 3,950,000 red blood cells, 60 per cent hemoglobin and 6,500 white blood cells. A blood culture was negative. The urine showed many red blood cells and a few granular casts.

The patient became progressively more anemic and more septic. Edema appeared in the legs and vulva and spread to the back. She complained of cough, epistaxis and occasional bloody diarrhea. A purulent vaginal discharge and petechiae over the body appeared. In November, she became stuporous and irrational, and died suddenly on December 2.

*Autopsy.*—The pericardium bulged slightly; it contained 40 cc. of fibrinous, flaky serum; the visceral and parietal layers showed shaggy, hairlike exudate, and some easily broken adhesions. The heart weighed 260 Gm. The right chamber was greatly enlarged, the apex being formed by the right ventricle. The right auricle was markedly distended and hypertrophied. The posterior auricular wall, near the orifice of the coronary sinus, had two saccular adhesions; nodular thickenings and nodules were also found. The right ventricle was greatly hypertrophied, with marked endocardial thickening. The pulmonary valve showed long, grayish vegetations. The left ventricle appeared normal. The myocardium, on section, showed irregular areas of fibrous change. The aortic cusps showed some calcification.

The lungs were congested posteriorly, with areas of partially consolidated tissue.

The spleen weighed 900 Gm. It was a dense purplish red, cut easily, and showed many follicles and no infarcts.

The liver weighed 2,000 Gm., was dense and firm, and had a marked nutmeg appearance.

The kidneys were normal in size and were dark purple, with mucus-like dots scattered through the zone glomeruli.

The condition was diagnosed as lobar pneumonia, glomerular nephritis, chronic passive congestion of the spleen and liver, fibrinous pericarditis and myocardial fibrosis.

#### DISCUSSION

C. DE LA CHAPELLE: This is an interesting and unusual case, and adds another one to the list of cases of congenital pulmonary stenosis associated with bacterial endocarditis. Judging by its gross appearance, it looks like a typical lesion of *Streptococcus viridans* endocarditis. The presence, however, of fibrinous pericarditis in *Streptococcus viridans* infection is unusual, about 0.5 to 1.5 per cent of the cases being associated with a pericardial lesion. Another unusual thing about the specimen, and which is often found in this valvular type of pulmonary stenosis, is the absence of associated congenital cardiac anomalies, especially a patent interventricular septum. In this case one would expect to find none of these other congenital anomalies, because of the relatively long life enjoyed by this patient.

WILLIAM C. VON GLAHN: I have had no experience with pulmonary stenosis of the congenital type. I should like to ask what organism was recovered.

HARRISON S. MARTLAND: Could not the endocarditis in this case be best classified as subacute bacterial of the indeterminate group of Libman? Such cases are frequently complicated by a pericarditis and give the vague bacteriologic manifestations seen in this case.

LOUIS FAUGERES BISHOP, JR.: I showed this patient to Dr. Libman, who told me that undoubtedly the condition must have passed through the indeterminate stage. On what grounds he based that I am not sure. The two blood cultures were negative. A Gram-Weigert stain was made, the vegetations being crushed, which showed what looked more like a round staphylococcus than *Streptococcus viridans*. The stain was unsatisfactory, and although some care was taken with it, it was not possible to determine the organisms. I understand that one should use not only the Gram-Weigert stain, but some of the others in order to bring out the organisms.

## Book Reviews

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LEHRBUCH DER ENTWICKLUNG DES MENSCHEN. VON DR. ALFRED FISCHEL, O. Professor der Embryologie und Vorstand des Embryologischen Institutes der Wiener Universität. Mitt 668 Z. T. Farbigen Abbildungen. Price, 86 marks. Pp. 822. Berlin: Julius Springer, 1929.

It is well recognized that many of the earlier stages of development of man are imperfectly known. The inclusion of earlier phases of the development of lower organisms not only fills the gaps in the knowledge of human embryology but at the same time serves to simplify many of the complexities encountered in human development. It is indeed a happy combination to find a text in which the general features of development receive adequate attention. Special topics are introduced to illustrate the various ramifications of the problem, and the details of human development are combined in one attractively printed volume, replete with excellent and wisely chosen illustrations. Professor Fischel's book is one of the most successful attempts to realize these ends that has recently appeared.

The interesting 15 page introduction and historical sketch of the development of the subject of embryology is followed by a discussion of general embryology of 250 pages (part 1), and an account of human organogeny of 550 pages (part 2). The arrangement of material is excellent; the stages of development are taken from the better known animal forms; the general principles of embryology are discussed in the proper place to make a coherent story of development; the illustrations are wisely chosen and beautifully executed.

The germ cells as the logical beginning of development are treated as dynamic elements. Their morphology and development concern live cells the activities of which are conditioned by certain physiologic states within and without the cells. They have a limited life and fertilizing capacity. The atypical cells are considered, and the inter-actions of the normal gametes in zygote formation is followed for different forms. Fertilization is both a means for the transmission of parental inheritance to the new organism and a means of initiating development. Chromosome behavior, the principles of genetics, parthenogenesis, polyspermy and the physicochemical changes following initiation of development receive attention. The general problems of organization, localization, and the prospective potencies of parts take the student below the surface of mere descriptive detail. Cleavage, germ-layer formation and the early appearance of the embryo are treated in a comparative manner with many illustrations coming from invertebrates but more attention centered on an ascending series of vertebrates including the lower chordates (amphioxus), amphibia, reptilia, apes and lower mammalia. The development of such a series of individual forms leads logically to the known or hypothetic similar stages in human development. A discussion of complete and incomplete twinning in different animals, and double human monsters, serves to further demonstrate developmental capacities. The formation of the embryonic membranes and delimitation of the embryos of many species is logically followed by a description of the earliest human embryos and by the problems of implantation and placentation. The description of the human membranes and placenta is again preceded by descriptions of these structures in lower mammals.

In part 1 the author has interspersed sufficient interpretation and philosophic deduction with demonstrations of fact to build up a well rounded presentation of the general features of development; the comparative development of different animal forms serves admirably to demonstrate these general features, and at the same time the account contains a great deal of detail for the development of the individual species. Under each separate topic of discussion the general development serves to introduce either the known or hypothetic condition of the develop-

ment of man. One greatly misses references to original sources, especially in part 1. A good bibliography would greatly enhance the value of the book for both the general and the special student. Many questionable statements cannot be referred to the original source for whatever special condition may have justified the statement. Some errors occur, but this is perhaps to be expected in a first edition.

Part 2 is concerned entirely with human organogeny. The development of the different germinal layers is followed from very early embryos, through the origin and development of the different organs. In some cases, more advanced differentiation of the organ substance is given, and even more attention to the later histogenesis would have been a distinct addition but perhaps beyond the scope intended for one volume. One of the more outstanding omissions of human development is that of the circulatory system, in particular the development of the post-caval system. Despite the completeness of the work of McClure and Butler (1925) on the development of the postcava in man, Fischel has illustrated the development only by schematic diagrams based on older and incomplete accounts.

The book is more complete in the general phases of development and the specific development of man than most treatises on embryology. For many it will be regretted that more attention was not given to malformations arising in embryonic development, as these find their explanations in peculiarities of development of certain parts. The most severe omission, to the special student, is undoubtedly that of a bibliography.

**THE KAHN TEST—A PRACTICAL GUIDE.** By R. L. KAHN, Sc.D. Price, \$4. Pp. 201. Baltimore: Williams & Wilkins Company, 1928.

In presenting the technic and fundamentals of the Kahn test in a well planned volume of about 200 pages including an up-to-date bibliography, Kahn has filled a need. His earlier volume, "Serum Diagnosis of Syphilis by Precipitation" deals largely with the historical and developmental phases of the test. As such it is well supplemented by this recent book. In the first place, much of the material presented in this book will be of value to those students of serologic problems who are eager for an understanding of the fundamental principles on which the Kahn test is based. At the same time the book fills the need of the serologic worker by giving precise directions for the various procedures in dealing with serum and spinal fluid, to each of which a chapter is devoted with a brief discussion of clinical interpretation. Although there is a certain amount of repetition of detail, outline form is frequently used, and numerous illustrative and summarizing tables are included.

Of particular interest to the serologist is the chapter on antigen standardization. In connection with this problem, Kahn has made an especially significant contribution. He introduces the use of a special sensitizing lipid extract, and presents experimental evidence for the quantitative dependence of antigen sensitiveness with syphilitic serum on the proportions of two types of lipid extracts in the antigen and the total concentration of lipids present. Practical application of this observation makes possible the correction of antigens with varying degrees of sensitiveness to the uniform "standard" sensitiveness required by the Kahn test. The same principle is also used in correcting "sensitized" antigens.

In the introductory chapter, consisting of sixty-four pages of text, tables and charts, Kahn takes a novel step toward translating the detailed studies on his own test from the particular to the more general. Presented in a manner that should appeal to the colloid chemist as well as to the serologist and syphilologist, these studies are now made available as a preliminary structure on which may be built a more fundamental understanding of the nature of the serologic reaction in syphilis. The "Practical Guide" should therefore arouse interest among a varied group of workers. To the serologist, whatever his opinions on the controversial subject of serum tests for syphilis, the book will be especially valuable.



SURGICAL PATHOLOGY. By CECIL P. G. WAKELEY, F.R.C.S. (ENG.), F.R.S. (EDIN.), and ST. J. D. BUXTON, M.B., B.S. (LOND.), F.R.C.S. (ENG.). Price, \$12.50. Pp. 904, with 392 illustrations. New York: William Wood & Company, 1929.

This book is intended to "put forward such an account of the pathological side of surgery as may help readers with their clinical work" and to help the undergraduate student, particularly in the study of specimens in the museums. There are seventy-five chapters dealing with a great variety of topics, ranging from bacteriology to shock, but for the most part with special descriptive pathologic anatomy. The presentation of the various subjects is brief and more in the way of succinct summaries or cataloguing of more or less generally accepted items of knowledge with avoidance of discussion of underlying principles, conflicting theories and unsettled questions. In many cases the chapters are so brief as to be of little significance except possibly by way of introduction to more comprehensive discussions. This is true particularly of the chapters dealing with bacteriology, infection and immunity, which consist of nine pages; inflammation, of eight pages; wounds, of five pages; erysipelas, of one-half page and tuberculosis of six pages. Giant-cell tumors of the bone are described (too briefly) under the name of myeloma, and the statements in the two places in which these growths are considered do not agree. Myeloma as ordinarily understood is discussed under the term myelomatosis. So-called carcinoid of the appendix, carcinoma of the prostate, melanoma and endometriosis are mentioned merely as examples of conditions that are not described fully enough. For the most part the illustrations are well selected, and many of them are original. A large number is credited to the *British Journal of Surgery*. In the case of figures 91, 92 and 93 it is not possible to discover the letters referred to in the descriptive legends. The book will be of use as a guide in the laboratory and museum, but it in no sense can take the place of standard works on pathology. The most valuable part lies in the illustrations.

# ARCHIVES OF PATHOLOGY

VOLUME 8

SEPTEMBER, 1929

NUMBER 3

## THE SO-CALLED SMALL ROUND CELL INFILTRATIONS

### II. SYPHILIS OF THE CENTRAL NERVOUS SYSTEM \*

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In a previous contribution on the subject of round cell infiltrations in polioencephalitis and acute epidemic encephalitis,<sup>1</sup> we were able to demonstrate that the vast majority of the infiltrating elements in the adventitial spaces, as well as those encountered in the extravascular territory, are constituted of emigrated lymphocytes, large mononuclears (monocytes) and homoplastic derivatives of the emigrated cells. It was pointed out that in none of the cases investigated was there any evidence of a cytogenic activity on the part of the fixed adventitial connective tissue or of vascular endothelium sharing in the production of the perivascular infiltrations. It was also shown that the emigrated lymphoid cells, after extravasation, varied in their behavior. Some of them remained unchanged as lymphocytes and large mononuclears; others differentiated into either polyblasts, macrophages or compound granular cells, and occasionally into plasma cells, the polyblasts being the prevailing cell type into which they were transformed.

### REVIEW OF LITERATURE

#### DERIVATION OF INFLAMMATORY MONONUCLEAR CELLS

Since the writing of our last paper, several interesting contributions have been made on the specificity and the alleged cytopoietic activity of

\* Submitted for publication, May 3, 1929.

\* Read before the Forty-Fifth Session of the American Association of Anatomists, Rochester, N. Y., March 27, 1929.

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\* This work was aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Michels, N. A., and Globus, J. H.: So-Called Small Round Cell Infiltrations: Polio-Encephalitis and Acute Epidemic Encephalitis, *Arch. Path.* 4:692 (Nov.) 1927.

the vascular endothelium. Thus, the contention of Foot and Herzog, that carbon laden endothelial cells may desquamate from the lining of small blood vessels and capillary tubes and become free ameboid cells, has been proved to be unwarranted by Lang<sup>2</sup> and by Stilwell.<sup>3</sup> The latter, repeating Herzog's experiment on the living frog, noted that the carbon particles passing through the fixed endothelium were taken up by adjoining mononuclear cells, which thereupon differentiated into free ameboid polyblasts. Lang<sup>4</sup> came to a similar conclusion in his studies on the inflammatory reactions of the connective tissue and the omentum in rabbits that had received intravenous injections of india ink. Earlier, in explants of lung inoculated with tubercle bacilli, Lang<sup>5</sup> observed that the dust cells, i. e., macrophages or epithelioid cells, took their origin not from the capillary endothelium but from small interlobar septal histiocytes.

Recently, Foot<sup>6</sup> retracted his views on the endotheliogenous derivation of large mononuclears. Lewis,<sup>7</sup> on using a supravital staining technic in the study of sterile inflammations of the deep fascia of the rat, found no evidence that mononuclears and macrophages are derived either from endothelium or connective tissue.

Clarke and Clarke,<sup>8</sup> studying the living cells and tissues in the transparent tail fin of amphibian larvae, stated that a desquamation of lymphatic endothelium occasionally took place, but that the process was "in no sense a proliferation of endothelium to form free leukocytes and wandering cells." They concluded, "In none of our observations on the normal growth of lymphatic and blood capillaries and on their behaviour under experimental conditions, such as inflammation, did we see the slightest evidences for the formation of 'endothelial leucocytes.'"

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2. Lang, F.: Rôle of Endothelium in the Production of Polyblasts (Mononuclear Wandering Cells) in Inflammation, *Arch. Path.* **1**:41 (Jan.) 1926.

3. Stilwell, F.: On the Phagocytic Capacity of the Blood Vessel Endothelium of the Frog's Tongue and Its Presumed Transformation Into Wandering Cells, *Folia haemat.* **33**:81, 1926.

4. Lang, F.: Ueber Gewebekulturen der Lunge, *Arch. f. exper. Zellforsch.* **2**:93, 1926.

5. Lang, F.: The Reaction of Lung Tissue to Tuberculous Infection in Vitro, *J. Infect. Dis.* **37**:430, 1925.

6. Foot, N. C.: Studies on Endothelial Reactions, etc., *Am. J. Path.* **3**:413, 1927.

7. Lewis, W. H.: Macrophages of the Deep Fascia of the Thigh of the Rat in Spreads Supravitally Stained with Neutral Red and with Janus Green, *Tr. Am. A. Anatomists*, 42nd session, New Haven Anat. Rec. **32**:215, 1926; Macrophages in Sterile Inflammation of Deep Fascia of the Rat, *ibid.* **32**:215, 1926.

8. Clarke, E. R., and Clarke, E. L.: On the Failure of Endothelial Cells, Even After Desquamation, to be Transformed into Wandering Cells, with Observations on the Nature of Endothelium, *Anat. Rec.* **36**:357, 1927.

Recently, Bloom,<sup>9</sup> a former assistant of Maximow, in an extensive treatise on the monocyte, categorically denied a histiocytic, especially a reticulo-endothelial, origin of the monocyte. His work was based on the monocytosis experimentally produced in rabbits by infection with *Bacillus monocytogenes* and by injections of india ink, lithium carmine and saccharated iron oxide. In his investigations, he used supravitaly stained smears of blood and of various organs, wet fixed smears of blood and of organs and sectioned material. He admitted a transformation of fixed embryonic reticulum cells into free macrophages, but insisted that these were not identical with monocytes. Differentiation of the latter proceeded from lymphocytes within the blood vessels, especially those of the spleen and the liver. The monoblast, as a specific stem cell (Ferrata, Sabin, Witts and Webb), does not exist. In his own words, "I have never observed any evidence of the direct transformation of any fixed cells, be they fibroblast or reticulum or endothelial cells of embryonic or mature nature into monocytes."

On the other hand, there is a notable array of recent investigations that reaffirm the endothelial activity. Thus, according to Oeller and Töppich, vascular endothelium is activated cytogenetically after anaphylactic shock. Oeller<sup>10</sup> maintained that in guinea-pigs rendered allergic through the injection of chicken erythrocytes, subsequent intravenous injections of antigen produced an intense and almost immediate (in from fifteen to thirty minutes), largely amitotic proliferation of the vascular endothelium in the lungs and other organs, the products being free ameboid cells, of which many differentiated into granulocytes.

A similar behavior of the vascular endothelium in guinea-pigs after intratracheal and intravenous injections of tubercle bacilli was described by Töppich.<sup>11</sup> Recently, Sabin, Doan and Cunningham,<sup>12</sup> by using the supravital technic on films of living cells, which were obtained by punctures of the spleen and the peritoneum of the living rabbit, and on spreads from the omentum and subcutaneous tissue, were able to detect

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9. Bloom, W.: The Origin and Nature of the Monocyte, *Folia haemat.* **37**:1, 1928; The Relationships Between Lymphocytes, Monocytes and Plasma Cells, *Folia haemat.* **37**:63, 1928.

10. Oeller, H.: Die funktionelle Bedeutung der Gefäßwandzellen bei akuten Infektionen, *Med. Klin.* **19**:97, 1923; Experimentelle Studien zur pathologischen Physiologie des Mesenchyme und seiner Stoffwechselleistungen bei Infektionen, *Krankheitsforschung* **1**:28, 1925.

11. Töppich, G.: Die zellulären Abwehrvorgänge in der Lunge bei Erst und Wiederinfektion mit Tuberkelbazillen, *Krankheitsforschung* **2**:15, 1925; Die örtliche Zellbindung in Gefäßwänden und im Bindegewebe, *München. med. Wchnschr.* **74**:135, 1927.

12. Sabin, F.; Doan, C., and Cunningham, R.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, *Contrib. Embryol.*, 82, Carnegie Inst., Washington **16**:125, 1925.

two distinct types of phagocytic cells, viz., clasmatocytes and monocytes. The former, they contended, were derived from the endothelium, mainly that of the spleen. They added, however, that "whether there is a widespread origin of clasmatocytes from the endothelium of the peripheral capillaries is not yet certain."

McJunkin,<sup>13</sup> on the basis of phagocytosis of india ink in vitro, peroxidase staining of smears and sections with benzidine, supravital staining with neutral red and injections of india ink, distinguished three types of phagocytes: (1) monocytes or benzidine-positive mononuclears, which are present in the blood, the bone-marrow and the spleen only; (2) lympho-endotheliocytes, benzidine-negative, which arise from the lymphatic reticulo-endothelium and are normally present in the blood stream; (3) hemendotheliocytes, benzidine-negative, which are normally absent in the circulation, but which appear under pathologic conditions, and which arise from the endothelium of capillary blood vessels.

Di Guglielmo<sup>14</sup> noted in the peripheral blood of patients with acute erythremia and streptococcemia large numbers of "endothelial phagocytes." These cells were distinct from monocytes and hemohistiocytes. They phagocytosed bacteria and showed mitotic proliferation. In his opinion, the vascular endothelium was responsible for their genesis and because of this he regarded their presence in large numbers in the circulating blood as warranting the term "endotheliosis." Di Guglielmo, describing the histologic changes observed in smears and sections of bone-marrow, spleen and liver in cases of erythremia and septicemia, maintained that in both conditions there was prevalent a generalized hypertrophy and hyperplasia of the reticulo-endothelial system, and that vessels of the lungs and kidneys exhibited hypertrophy and detachment of vascular endothelial cells, which, when free in the lumen of the vessels, acquired a phagocytic function. The author contended that since they were morphologically identical with those observed in the peripheral blood, the cytopoietic and functional activity of the vascular endothelium is general and hence it should be regarded as part of the reticulo-endothelial system.

Fontana,<sup>15</sup> in his extensive monograph on endocarditis lenta, maintained that in 39 per cent of the cases investigated by him the first drop of peripheral blood obtained soon after rubbing an area punctured

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13. McJunkin, F. A.: Identification of Three Types of Mononuclear Phagocytes in the Peripheral Blood, *Arch. Int. Med.* **36**:799 (Dec.) 1925.

14. Di Guglielmo, G.: La patologia e la clinica del sistema reticolo-endoteliale, *Haematologica* **7**:481, 1926.

15. Fontana, F.: Ricerche su di uno speciale reperto ematologico nella endocardite lenta e su reperti affini in varie altre condizioni, *Haematologica* **7**:271, 1926.

(notably in the ear region) showed the presence of endothelial and lymphocytoid cells, which frequently showed phagocytic properties. Successive drops contained fewer of these structures and when no rubbing preceded the procuring of blood, they were sparse or entirely lacking. They commonly occurred in ratios varying from 0.5 per cent to 18.2 per cent, but sometimes attained a ratio of 34.3 per cent. In similar preparations of blood from twelve normal persons and from ninety-eight patients with diseases other than endocarditis lenta, the endothelial elements were extremely sparse and more often lacking entirely. Their presence in a relatively high ratio in endocarditis lenta was believed to be pathognomonic of this disease. The proliferation and desquamation of the peripheral capillary and precapillary endothelium was thought to be their source of origin.

Schilling,<sup>16</sup> on the basis of transitional stages between histiocytes and monocytes in the blood in cases of endocarditis lenta and monocytic leukemia and on that of identical negative oxydase reactions and phagocytosis in the two cells, derived the monocytes from the stellate Kupffer cells of the liver.

Esposito,<sup>17</sup> studying twenty cases of typhoid fever, encountered a limited number (from one to three, or 0.5 per cent) of circulating "reticulo-endothelial" elements. Previous rubbing of the area from which the blood was taken (ear), however, did not increase their ratio (Fontana) and hence he concluded that a local origin of the structures from vascular endothelium is highly improbable.

Capocaccia,<sup>18</sup> with repeated massive injections of trypan blue and oxy-saccharate of iron oxide into rabbits and guinea-pigs, obtained a monocytosis, the endothelial forms of which he assumed to be products of vascular endothelium.

According to Masugi,<sup>19</sup> a pupil of Aschoff, an initial storing of colloidal substance causes a proliferation of the reticulo-endothelial system, but later when the entire system is actively storing, leading to a "blockade," desquamation with formation of monocytes takes place. Mature, dye-storing histiocytes, however, never participate in the production of monocytes.

16. Schilling, V.: Der Monocyte in trialistischer Auffassung und seine Bedeutung im Krankheitsbilde, *Med. Klin.* **22**:563, 1926.

17. Esposito, A.: Sulle cellule reticolo-endoteliali nel sangue circolante dei tífosi, *Haematologica* **9**:157, 1928.

18. Capocaccia, M.: L'apparato reticolo endoteliale; le modificazioni del quadro ematologico negli animali trattati con iniezioni di trypanblau e di saccarato ossido di ferro, *Haematologica* **8**:321, 1927.

19. Masugi, M.: Ueber die Beziehungen zwischen Monozyten und Histiocyten, *Beitr. z. path. Anat. u. z. allg. Path.* **76**:396, 1927.

Claussen,<sup>20</sup> studying miliary tuberculosis of the kidneys in cows and pigs, found that the endothelial cells of the interlobular capillaries were (in addition to the histiocytes) participating in the formation of the epithelioid cells characteristic of the tubercles.

The subject of so-called endotheliocytopoiesis became recently somewhat more clouded by the amazing contentions of von Möllendorff,<sup>21</sup> and his students Koll<sup>22</sup> and Knake,<sup>23</sup> who asserted that fixed fibroblasts are mainly responsible for the genesis of the various types of the free cells found in inflammatory conditions.

Von Möllendorff's opinion is based on the observations made on the inflammatory reaction of loose connective tissue in mice and rabbits following subcutaneous injections of trypan blue. The loose connective tissue, in his opinion, consists of an abundantly meshed fibrocyte network containing numerous resting wandering cells. The latter are attached to the net by fine strands which, in inflammatory conditions may break and so release the cells, which transform themselves into macrophages. Tissue leukocytes, also, he said, are similarly generated from the net through vacuolization in the nuclei of fibroblasts and differentiation of cytoplasmic granules. In acute inflammations, a widespread breaking up of the net takes place with the resulting formation of many round cells (polyblasts). These in a large measure differentiate into polymorphonuclears which soon undergo degeneration. A number of surviving large cell types (histiocytes) regenerate the syncytium by spreading out and by amitotic proliferation. The adventitial cells are not parent cells in the sense of Marchand, but represent simply a more or less torn portion of the fibrocytic net. Thus, von Möllendorff would consider the connective tissue as morphologically and biologically identical with that of the reticulo-endothelial system.

Koll, using subcutaneous injections of Patentblau, noted that in mice the "inflammatory centers" showed an immediate degeneration of the original leukocytes, which was followed by a decided heteroplastic regeneration of the leukocytes from fibroblasts by a rounding up of histiocytes. Two days later, changes in the newly formed leukocytes gave rise to

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20. Claussen: Untersuchungen über die Histogenese des Nierentuberkels, Virchows Arch. f. path. Anat. **266**:456, 1927.

21. Von Möllendorff, W. and M.: Das Fibrozyten-Netz im lockeren Bindegewebe seine Wandlungsfähigkeit und Anteilnahme am Stoffwechsel, Ztschr. f. Zellforsch. u. mikr. Anat. **3**:503, 1926; Die örtliche Zellbildung in Gefässwänden und im Bindegewebe, München. med. Wchnschr. **74**:135, 1927.

22. Koll, W.: Bindegewebsstudien: II. Die Wirkung von Patentblau auf das Unterhautbindegewebe der Maus, Ztschr. f. Zellforsch. u. mikr. Anat. **4**:702, 1927.

23. Knake, C.: Bindegewebsstudien; die Histo- und Leukozytenentstehung bei Tuschewirkung auf das lockere Bindegewebe des Kaninchens, Ztschr. f. Zellforsch. u. mikr. Anat. **5**:208, 1927.

macrophages. But, in his conclusions, he said that "the rôle played by emigration in the increase of leukocytes was not investigated."

Knake maintained that in rabbits, after subcutaneous injections of india ink, dye-laden fibroblasts rounded themselves up and differentiated into histiocytes and round cells, both of which might develop into polymorphonuclear leukocytes through a differentiation of eosinophil granules and a gradual liberation of carbon particles. At the beginning of the inflammatory process, the walls of the small veins showed a marked "transformation" into round cells; in addition to the "completer" leukocytes, numerous intergrades were present. While he did not exclude the possibility of an emigration of leukocytes (which he regarded as still an open question), he favored a local origin of the inflammatory cells through differentiation and amitotic proliferation of fibroblasts. In respect to emigration, Knake stated, "Wie gross demnach wirklich die Anzahl der 'emigrierten' Leukocyten ist, lässt sich vorerst nicht abschätzen." (It cannot yet be estimated how large the number of emigrated leukocytes really is.)

This view of von Möllendorff and his students as to the polyvalent hemohistiopoietic potencies of the fibroblasts has since received a decided and well merited check. Using von Möllendorff's own technic, Maximow<sup>24</sup> conducted control experiments, compared his results with von Möllendorff's original slides and concluded that "new facts were not discovered." Subcutaneous injections of trypan blue or india ink revealed the familiar pictures of an inflammatory reaction to a soluble or a particulate foreign substance. Nothing was observed that could suggest the possibility of the origin of leukocytes from fibroblasts.

More recently von Möllendorff, to substantiate his claim, conducted a series of experiments. In collaboration with Burger,<sup>25</sup> he separated the jugular vein from surrounding tissue, ligated it and then introduced various irritating substances. Sections of this vein were then explanted. Within an hour there resulted a strong leukocytosis in the wall and in perivascular spaces with a transformation of endothelium and vascular connective tissue elements into leukocytes. No difference was observable between cultured and noncultured sections.

Gerlach and Jores,<sup>26</sup> repeating von Möllendorff's experiments, emphatically denied the latter's contention. Irritants, such as lamb serum, turpentine or jequiritol III, were introduced into the jugular vein

24. Maximow, A.: Morphology of the Mesenchymal Reactions, Arch. Path. 4:567 (Oct.) 1927.

25. Von Möllendorff, W.: Die örtliche Zellbildung in Gefässwänden und im Bindegewebe, München. med. Wchnschr. 74:135, 1927.

26. Gerlach, W., and Jores, A.: Die Herkunft der Exudatleukocyten bei der akuten Entzündung, Virchows Arch. f. path. Anat. 267:551, 1928.



in guinea-pigs. After a double ligation, portions of the vein were investigated at various intervals of from one to ten and three-quarter minutes; others were explanted. In both, the sequence of events was as follows: aggregation of blood cells, stagnation, marginal attachment of leukocytes to endothelium and subsequent emigration of these out into the tissue. Neither the vascular endothelium nor the constituents of the vessel wall gave rise to an exudate of leukocytes. Similar results were obtained in sensitized rabbits rendered aleukocytic through repeated subcutaneous injections of benzol-olive oil and in untreated rabbits rendered poor in leukocytes through subcutaneous injections of staphylococci, jequiritol I and turpentine. The excised tissues showed no evidence of a local origin of the leukocytic exudate. Their presence about the vessels and in the surrounding tissues (at times, marked) must be traced to hemic elements that reached the site of inflammation by diapedesis.

Thus, the discussion as to the derivation of the inflammatory mononuclear cells has, for the present, shifted from the endothelium to the fibroblasts, von Möllendorff, attempting, as Maximow put it, "to revolutionize completely the dominant ideas on the morphology of local defense reaction."

#### HISTOLOGIC CHANGES IN SYPHILITIC DISEASES OF THE CENTRAL NERVOUS SYSTEM

As material for our second paper on the small round cell infiltration, we have selected various types of syphilitic diseases of the central nervous system.

Difficult and markedly polemic have been the steps leading to the present knowledge of the histologic changes in these diseases. Syphilis, in particular, came in for considerable discussion, because cases were frequently reported in which the important evidence of a preexisting primary lesion was either entirely lacking or not sufficiently substantiated. On the other hand, instances of known nonsyphilitic origin in which the clinical pictures simulated those of paresis were frequently mistaken for syphilis. Finally, the possibility of a co-existing nonsyphilitic form of encephalitis in cases of known or doubtful syphilis was not sufficiently taken note of.

*Alzheimer's Views Concerning Paresis.*—The pioneer and still dominant work in the establishment of the histologic features of paresis and of meningovascular syphilis is the monograph of Alzheimer.<sup>27</sup> It is based on a study of 320 cases of various brain disturbances, 70 of which were diagnosed clinically as paresis. Since this work is not

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27. Alzheimer, A.: Histologische Studien zur Differenzialdiagnose der progressiven Paralyse, in *Histologische und Histopathologische Arbeiten über die Grosshirnrinde*, Jena, Gustav Fischer, 1904, vol. 1, pp. 18-314.

generally known to the general pathologist or anatomist, a résumé of Alzheimer's views is hereby given as an introduction to our own observations.

Alzheimer emphasized the fact that syphilis cerebri presents no uniform histologic picture, while the anatomic alterations in paresis are so characteristic that even in the absence of a clinical diagnosis one can readily identify this disease. The latter is a chronic inflammatory process, and exhibits in all instances a widely distributed, fairly uniform adventitial infiltration with plasma cells and lymphocytes throughout the cerebral cortex. It is also characterized by changes in the vessels, hypertrophy of the intima, formation of endothelial sprouts, glial hypertrophy, degeneration of nerve fibers and fiber tracts and formation of rod cells. These changes may occur also in the brain stem, including the basal ganglions, thalamus, midbrain, pons and medulla oblongata; but, in these areas, their origin is not fully established.

The essential process of paresis, as understood by Alzheimer, is a degeneration of the parenchyma of the central nervous system, associated with progressive and regressive changes in the blood vessels. It is typified by the following alterations:

1. Hypertrophy of the endothelium with a marked tendency to the formation of new vessels through budding of the hypertrophied intima. As a result there is a marked increase of the number of blood vessels, more pronounced in some cases than in others. It is never lacking, save in the acute stages of the disease.

2. An increase of the elastic tissue with a formation of new meshes around the swollen endothelium, resulting in the formation of stronger walls.

3. Hypertrophy of the adventitia. This is always present, and is sometimes pronounced.

4. Widening and infiltration of the adventitial spaces. Most abundant among the infiltrating elements are the plasma cells; they are never lacking, not even in the acute type of the disease. Next in frequency are the lymphocytes, with mast cells occurring as isolated units.

5. Regularly a regressive change is noted in many of the vessels, especially those in marginal zones of the cortex. It may lead to a complete obliteration of the vessel and a hyalinization of its walls. If the latter occurs it is a secondary phenomenon.

6. Rod cells are constant in the cortex and their presence is pathognomonic of the disease. (Alzheimer's view that they originate from the vessels has since been definitely abandoned, their microglial derivation having been established.)

Most pronounced among the changes in the ectodermal structures is the marked hyperplasia and hypertrophy of the glia cells. These, in turn, give rise to an increase of glia fibers. The newly formed glia strengthens the walls of the blood vessels and gives rise to a thicker covering over the surface of the cortex. In advanced cases, the glia hems in the already heavily infiltrated vessels. Regressive changes occur also in the glia cells, which undergo sclerosis, pigmentation and

vacuolization. Necrobiosis of nerve cells, according to Alzheimer, leads to a gradual disappearance of the cortical fiber tracts. This is so characteristic that it may be regarded as specific for paresis. Topographically, the disease progresses along nerve tracts, resulting frequently in degeneration of definite fiber tracts in the cisternal area. Rapid disintegration of nerve cells and early replacement with massive glia hypertrophy is characteristic of paresis.

Meningeal changes are a constant phenomenon. No case of paresis is entirely free of them, though in the earlier stages of the disease pial thickening and infiltration need not necessarily be marked. The pial changes consist of hypertrophy of the endothelium, partial regressive changes in vessels and isolated new formation of capillaries. There is a massive increase of collagenous fibers, and hypertrophy of fibroblasts, some of which show regressive changes. In the arachnoid meshes and about the pial blood vessels there are infiltrating elements, most predominant among which are the plasma cells; some of these show signs of metamorphosis and vacuolization of their cytoplasm, simulating gitter cells. Mixed with the plasma cells are lymphocytes, mast cells and occasional well formed gitter cells. Polymorphonuclears are few or lacking.

These histologic changes were strikingly stereotyped in 170 cases clinically diagnosed as paresis. For syphilis cerebri, the situation is entirely different; here no uniform picture is found. This, as explained by Alzheimer, is due to the fact that in this disease the lesions in the cerebral cortex are not essentially primary as in paresis, but secondary. They appear to be subsequent to a previous pial disturbance. It is for this reason that in syphilitic meningitis the cortical layer next to the pia is most affected and the lesions gradually become less and less frequent as they recede from the periphery. Once brain tissue is involved, however, the lymphocytic infiltration advances rapidly and may quantitatively surpass that of paresis. Thus in meningovascular syphilis the degree of infiltration is much greater than in the severest form of paresis. The infiltration may be so marked as to obliterate all boundaries between the pia and the cortex, a condition best explained by the fact that the exudative cells do not, as in paresis, retain a perivascular habit, but filter out into neighboring tissue. If, however, the meningeal alterations remain restricted, changes in the cortex are correspondingly limited.

In syphilis cerebri there are also a new formation of vessels, a swelling of the intima, an increase of adventitial cells, a hyperplasia and hypertrophy of glia cells and a degeneration of ectodermal components. The typical plasma cells, according to Alzheimer, are decidedly less frequent in this disease than in paresis, their place being taken by a cell type intermediate between the lymphocyte and the plasma cell.

Appended to Alzheimer's work is the equally important contribution by Nissl,<sup>28</sup> in which he presented views substantially in agreement with those of Alzheimer. Nissl took up the problem of the origin of the infiltrating cells and evaluating the then prevalent theories as to their histogenous or hematogenous origin, he said that since a transformation of hypertrophied vascular connective tissue cells (endothelium, adventitial cells) into lymphocytes or plasma cells was never encountered in the extensive material investigated by him, the exudate cells must be regarded as hemic in origin; i.e., they represent emigrated lymphocytes, the plasma cells being special differentiation products of the latter.

As against Havet's<sup>29</sup> contemporary contribution that plasma cell infiltrations may be encountered in disturbances of the brain other than paresis, Nissl maintained that in his study of over 200 such cases he was unable to find a single instance presenting a typical infiltration with plasma cells. Conceding the point that the occurrence of the latter of itself is not necessarily pathognomic of paresis, the absence of plasma cells, in his opinion, certainly rules out paresis.

*The Plasma Cell.*—Since the plasma cell holds an important place among the infiltrating elements in the cases to be described, a short review of the literature on this type of cell is hereby given.

The morphology, genetic relationship and pathologic significance of the plasma cell have been the objects of considerable investigation and discussion. The extensive literature is highly controversial, as readily may be seen from the comprehensive review of this subject by Downey.<sup>30</sup> In summarizing the data, it may be noted that the term plasma cell was first used by Waldeyer in 1875 to describe certain types of connective tissue cells that gave a deep staining reaction with the then newly discovered basic aniline dyes of Ehrlich. The term, as now applied, was first used by Unna<sup>31</sup> in his description of cell elements encountered in lupus of the skin, though one year previously Ramon y Cajal<sup>32</sup> had independently called attention to the cell type, the representatives of which he then termed the chromatophil or cyanophil elements.

28. Nissl, F.: Zur Histopathologie der paralytischen Rindererkrankung, in Alzheimer: Histologische und Histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1904, vol. 1, pp. 315-494.

29. Havet, T.: Des lésions vasculaires du cerveau dans la paralysie générale, Bull. Acad. roy. de méd. de Belgique (4 série) 16:503, 1902.

30. Downey, H.: The Origin and Structure of the Plasma Cell of Normal Vertebrates, Especially of the Cold Blood Vertebrates, and the Eosinophils of the Lung of Amblystoma, Folia haemat. 11:275, 1911.

31. Unna, P.: Ueber Plasmazellen, insbesondere beim Lupus, Monatsch. f. prakt. Dermat. 19:465, 1891.

32. Ramon y Cajal, cited from Ferrata: Le Emopatie, Milano, Societa Editrice Libreria, 1918.

Unna originally defined the plasma cell as an extremely large structure having a deeply basophil protoplasm with a typical, fine, nonmetachromatic granulation (granuloplasm). He regarded it as a hypertrophied connective tissue cell found only under pathologic conditions, mainly in chronic inflammatory reactions.

Marschalko,<sup>33</sup> making his observations on normal, pathologic and experimental material, further delimited the term. He characterized the cell as containing (1) a nonhomogenous basic protoplasm with frequent paranuclear semilunar lighter staining areas, and (2) an eccentric position of the nucleus, which encloses angular blocks of chromatin (from 5 to 8), arranged in a circle about the nuclear membrane. Since these patterns of the chromatin were similar to that of the spokes of a wheel, Pappenheim advocated the term "Radkern." Though upholding Unna's specificity of the plasma cell, Marschalko differed with him in regard to its origin. In the opinion of Marschalko, plasma cells represented transformed emigrated lymphocytes; and their formation was not necessarily pathologic. In his opinion, they represented normal constituents of the connective tissue and the blood-forming organs. Jolly (1900) was among the first to confirm this view in his assertion that the cells could easily be demonstrated in peritoneal membranes.

The opposing views of Unna and Marschalko led subsequent investigators to take the following positions regarding the origin of the plasma cell: 1. A histogenous origin from connective tissue cells (Unna, 1891-1907; Ramon y Cajal, 1906; Veratti, 1905; Marchand, 1901; Dominici; Foa, 1902; Greggio; Ferrata, 1918; Joannovice, 1889 [only partly]). 2. A hematogenous origin from emigrated lymphocytes (Baumgarten, 1890; Helly; Krompecher, 1898; Marschalko, 1895; Nissl, 1904; Jolly, 1923, and Naegeli, 1919). 3. Mixed origin from emigrated lymphocytes or pre-existent tissue lymphocytes (Ribbert, 1897; Joannovice, 1899; Pappenheim, 1901; Maximow, 1902; Schridde, 1905; Weidenreich, 1911; Downey, 1911; Dubreuil and Favre, 1920; Bloom, 1928).<sup>34</sup>

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33. Marschalko, T.: Ueber die sogenannten Plasmazellen, ein Beitrag zur Kenntnis der Herkunft der entzündlichen Infiltrationszellen, Arch. f. Dermat. u. Syph. **30**:241, 1895.

34. A more complete review of the literature will be found in the paper by Downey (footnote 30) and in the following: Weidenreich, F.: Die Leukocyten und verwandte Zellformen, Wiesbaden, J. F. Bergmann, 1911; Ztschr. f. d. ges. Anat., p. 3; Ergebn. d. Anat. u. Entwicklungsgesch. **19**:527, 1911. Ferrata, A.: Le Emopatie, Milano, Societa Editrice Libreria, 1918, vol. 1, and 1923, vol. 2, (parte speciale). Jolly, J.: Traite technique d'hématologie, Paris, A. Maloine et fils, 1923. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923. Maximow, A.: Bindegewebe und blutbildende Gewebe, Handbuch der Mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 2, Die Gewebe, pt. 1.

The fibroblastic origin of the plasma cells as suggested by Unna and Cajal has never been fully established. The question of their origin from clasmatocytes, resting wandering cells, adventitial cells or hemohistio-blasts is one intimately associated with the problem of the tissue lymphocytes. But since, as Maximow in his recent work conclusively showed, the modern hematologists need no longer distinguish between histogenous and hematogenous lymphocytes, the origin of the plasma cell may definitely be traced to the differentiating small and medium-sized lymphocytes, monocytes and polyblasts, which acquire a deep basophilia, especially in the peripheral zone of the cytoplasm, and develop a lighter staining paranuclear area. The latter, according to Maximow (1902), Weidenreich, Wallgren and Jolly, constitutes a sphere of attraction for the cell's centrosome group as demonstrated by iron-hematoxylin staining.

The "Radkern" pattern of the nucleus (Marschalko) and the eccentric position of the nucleus were soon discarded as essential features. While the plasma cells are particularly numerous under pathologic conditions, the observations of Jolly, Maximow, Weidenreich, Downey, Ferrata and others have shown that they are a normal component of the general connective tissue particularly that of the omentum and of the blood-forming organs. They are frequently found in the mucosa of the digestive tract, as well as in the interstitial tissue of various glands and organs (mammary, submaxillary, tonsils, liver, kidney). In respect to the origin of the massive aggregates of plasma cells in chronic inflammatory conditions, Jolly (1923) held that "it must be admitted that the lymphocytes from which they are formed have come from the blood by diapedesis." An identical position was held by Maximow (1927) in the statement that in the foci of small cell infiltrations in chronic inflammations there are lymphocytes with transitional forms in the process of plasma cell formation.

It may be added that Weidenreich and Downey believed that the plasma cells are but temporal functional stages of the lymphocytes, while Jolly, Maximow and others contended that the cells are transient structures in the sense that they are brought into existence only to undergo degeneration, often resulting in the production of acidophilic bodies, commonly known as Russell bodies.

## OBSERVATIONS

### MATERIALS AND METHODS

The material for the present studies consisted of a group of seven cases, three of which were clinically diagnosed as chronic parenchymatous syphilitic encephalitis (paresis), three as meningovascular syphilis and one as vascular syphilis cerebri.

Numerous blocks of tissue were taken from various parts of the brain and spinal cord, including the cerebrum, midbrain, cerebellum, pons, medulla and, in some instances, the hypophysis, semilunar ganglion and dura mater.

Most of the material was fixed in formaldehyde. In one case, Zenker's fluid was used. The paraffin embedded blocks were sectioned at an average thickness of 5 microns. Delafield's hematoxylin followed by the azure-eosin combination as employed by Maximow was the staining method. Sections were placed in a

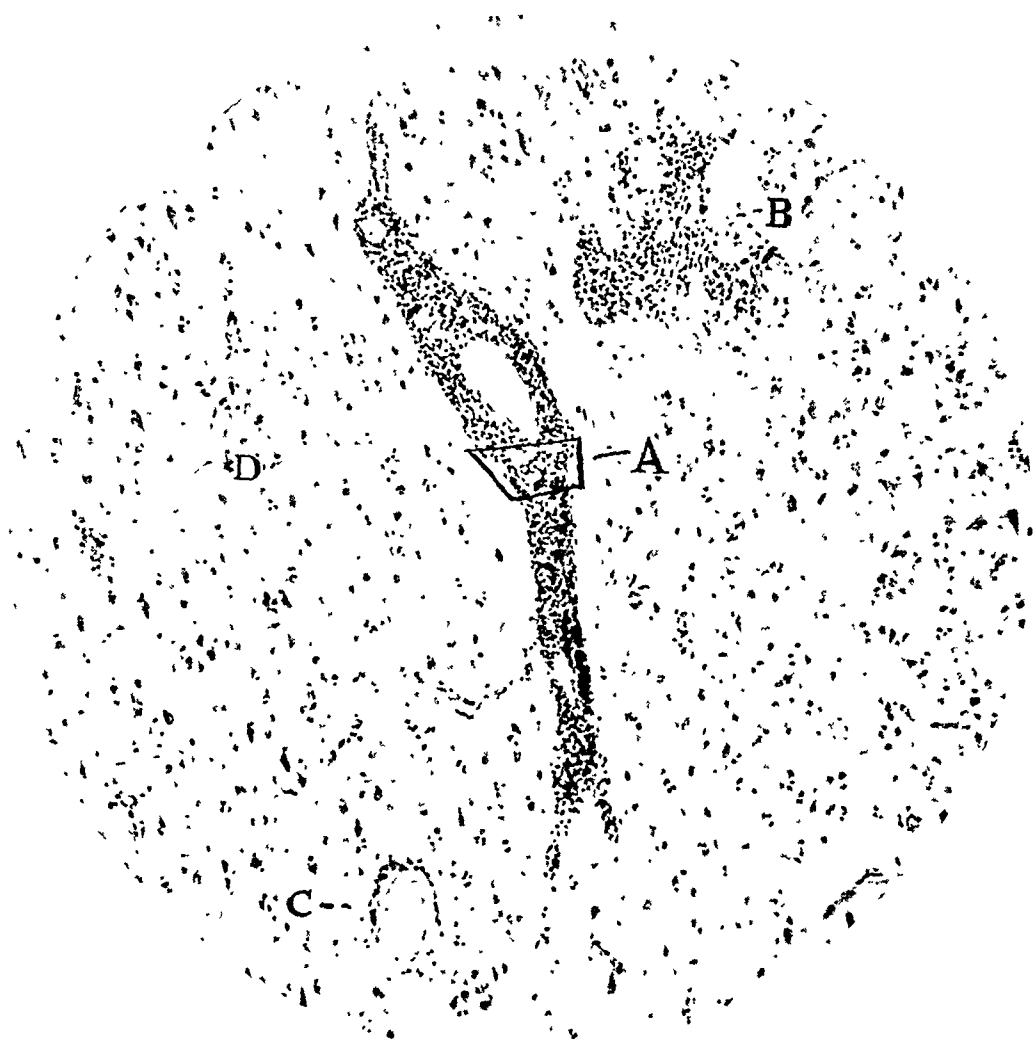


Fig. 1 (case 1).—Typical maximal infiltration in chronic parenchymatous syphilitic encephalitis. The region designated *a* appears again in figure 2; *b* indicates a new formation of capillaries with an infiltration of ameboid lymphocytes, polyblasts and plasma cells; *c* indicates an infiltration from two to three cell rows in depth; *d* indicates a new-formed capillary;  $\times 100$ .

diluted solution of hematoxylin (wine color) over night, washed the following day (for from eight to ten hours) in distilled water and transferred over night into the following stain: azure II in 1:1,000 solution, 9 cc.; eosin W. G. (Grübler) in 1:1,000 solution, 17 cc.; distilled water, 100 cc. Sections were differentiated in 95 per cent alcohol, dehydrated in two changes of absolute alcohol cleared in two changes of xylene and mounted in dammar.

CASE 1. CHRONIC PARENCHYMATOUS SYPHILITIC ENCEPHALITIS  
(PARESIS)

The perivascular infiltrations here frequently attain the intensity encountered in poli-encephalitis and acute epidemic encephalitis (figs. 1 and 2). Striking features, however, are the nonlymphoid aspect of the general parenchyma, the absence of the streamlike orientation of migrated lymphoid cells away from the vessels and the decided alteration in the architectural organization of the cortical layers caused by a widespread new formation of capillary tubes.

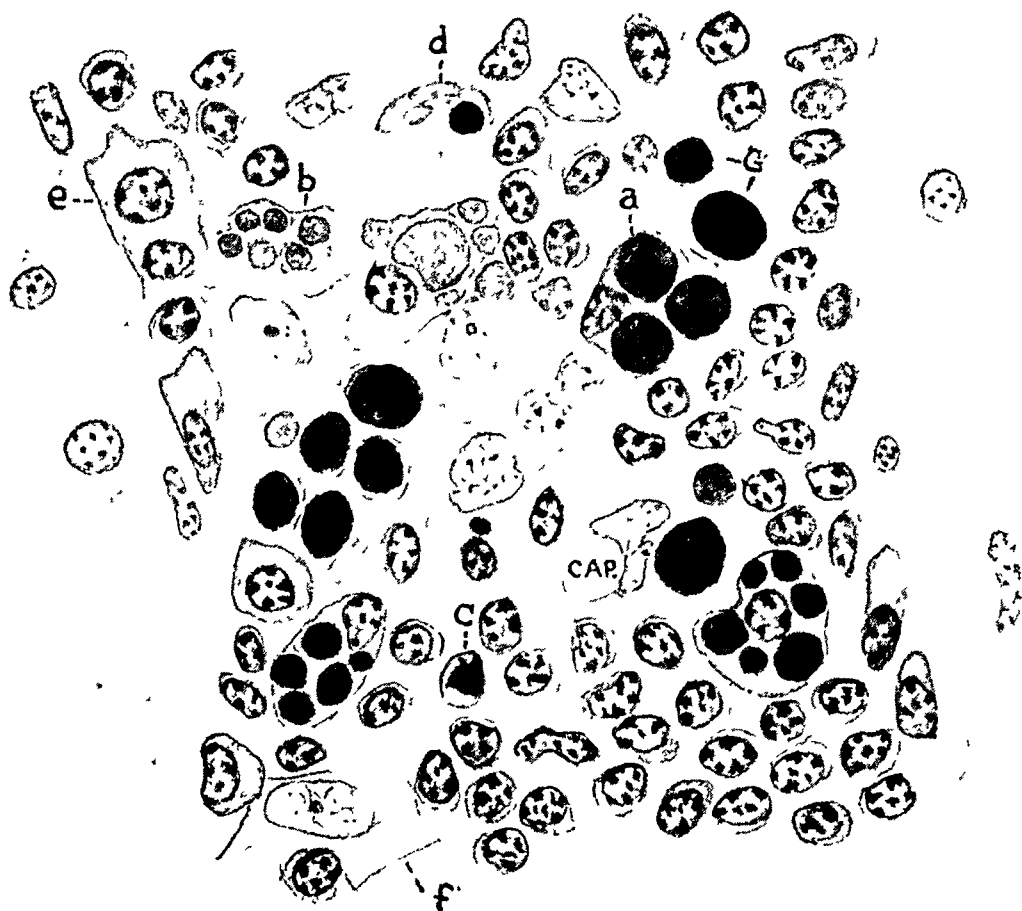


Fig. 2.—The area marked *a* in figure 1. The letters *a*, *b*, and *d* designate Russell bodies enclosed in degenerating plasma cells; *c* a dividing plasma cell; *f* a detached endothelial cell assuming the fibroblast form, and *g* free Russell bodies.

The maximal infiltrations reach a depth of from eight to ten rows, somewhat less therefore than that seen in poli-encephalitis, in which as many as fifteen rows are often encountered. While the precapillary venules average from two to four rows, the capillaries show more often the single row of infiltration. Such single rows are for the most part intermittently interrupted (figs. 3, 4 and 5). Not infrequently, therefore, stretches of capillary tubes may be seen in which infiltrating elements are extremely sparse or lacking. This is particularly true of the recently formed capillaries (figs. 5 and 6).



Initial infiltrations are best observed in the capillary regions (fig. 3). In poli-encephalitis, the single row infiltrations consist predominantly of small lymphocytes and present a uniform marginal radial seriation, but here they contain nearly exclusively plasma cells, two or three of which are, as a rule, disposed about cross sections of capillaries in a semicircular fashion (fig. 25 *A*). In longitudinal view, their habitat frequently appears as in figure 5, where the cell (*a*) either completely overlaps the capillary wall or (*b*) covers the vessel only partially. This seems to



Fig. 3—A capillary showing an initial infiltration mainly with plasma cells. The letter *a* indicates a plasma cell, *b* a detached endothelial cell, *c* a hypertrophied endothelial cell, *d* a small lymphocyte and *e* a glia cell;  $\times 1,200$ .

indicate that in initial infiltrations the plasma cells tend to remain in close proximity to the endothelial wall (fig. 3).

The plasma cells are extremely polymorphous. Their nuclei are usually round, often oval; most frequently they are eccentric in position. The cell bodies are frequently oblong in outline, often simulating the so-called adventitial cells of Marchand. They also assume spindle, box and triangular shapes. When closely packed, they are usually polygonal, but when separated, they show the spherical form.

Isolated mast cells are frequently found in initial infiltrations (fig. 25 *A*). In the absence of mesodermal elements, other than the endothelial cells, which do not form mast cells, they are in all probability hemic in origin and represent a differentiation product of the plasma cells. They are the so-called plasmamast cell of Krompecher,<sup>35</sup> which was also described by Marschalko, Pappenheim, Weidenreich, Downey and recently by Dubreuil and Favre<sup>36</sup> (1921). While in some instances mast cells are situated close to the endothelium and simulate the fixed histogenous form of mast cell (fig. 5) they, nevertheless, in the majority of cases, retain some features of their previous plasma cell morphology; the polygonal contour of the cytoplasm, the lighter, usually nongranular perinuclear area and the characteristic eccentric position of the nucleus (fig. 25 *B*). Similar structures are also observed in the larger infiltrations.

The sparsity of lymphocytes in the initial infiltrations may be explained by the probability that immediately after diapedesis the lymphocytes change into plasma

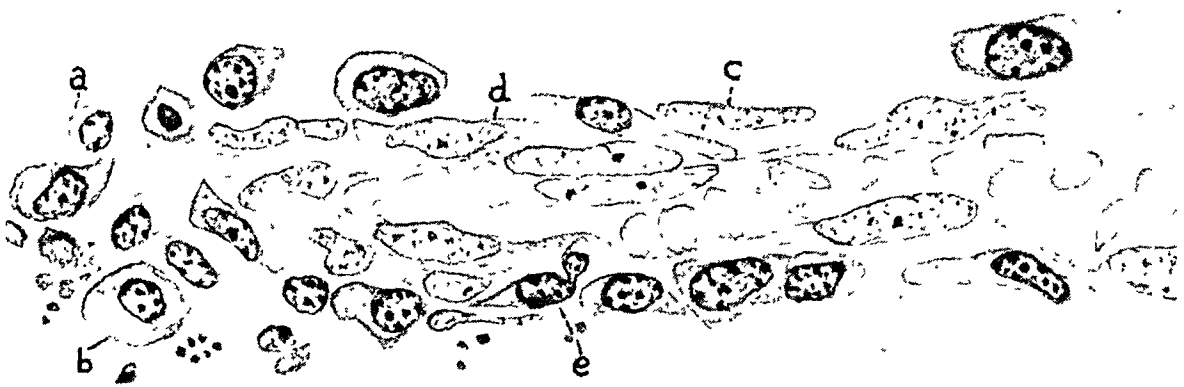


Fig. 4.—Initial infiltration; *a* indicates a degenerating small lymphocyte or plasma cell, *b* a degenerating plasma cell, *c* a detached endothelial cell retaining its normal form, *d* a detached endothelial cell undergoing change into a fibroblast-like structure, and *e* a recently emigrated large mononuclear changing into a plasma cell.

cells. This is supported by the observation that the protoplasm of the lymphocytes, while in transit through the capillary wall or immediately thereafter, often assumes a deeper basophilia (fig. 5 *d*).

Lymphocytes are more numerous in the more intensive infiltrations (fig. 7). When the latter attain the proportion of from four to six rows, lymphocytes constitute approximately half of the infiltrating elements. In the maximal infiltrations (ten or more rows), lymphocytes abound and frequently exceed the number of plasma cells (fig. 2). These small and medium sized lymphocytes predominate

35. Krompecher, E.: Beiträge zur Lehre von den Plasmazellen, Beitr. z. path. Anat. u. z. allg. Path. **24**:163, 1894.

36. Dubreuil, G., and Favre, M.: Cellules plasmatique, plasma granulations spécifiques, cellules a corps de Russell. Arch. d'anat. micr. **17**:302, 1920-1921.

(figs. 2 and 7) and there are but few large lymphocytes or large mononuclears, a decided departure from what is observed in poli-encephalitis and acute epidemic encephalitis. In paresis, the larger types of cells are mainly plasma cells, suggesting the probability that the extravasated lymphocytes undergo rapid differentiation into plasma cells. This explains the presence of many small and medium-sized lymphocytes in which the deeply basophilic protoplasm, the perinuclear portion of which is varyingly lighter in staining reaction, seems to indicate transitional stages between lymphocytes and plasma cells (fig. 7). In this process of transformation, the nucleus is commonly displaced from its central position, its chromatin is broken up into triangular masses, which are radially disposed and lodged against the nuclear membrane, thus presenting the typical nuclear pattern of Marschalko. However, it may retain its original contour. Since there are lymphocytes that acquire the typical nuclear form of Marschalko but retain the

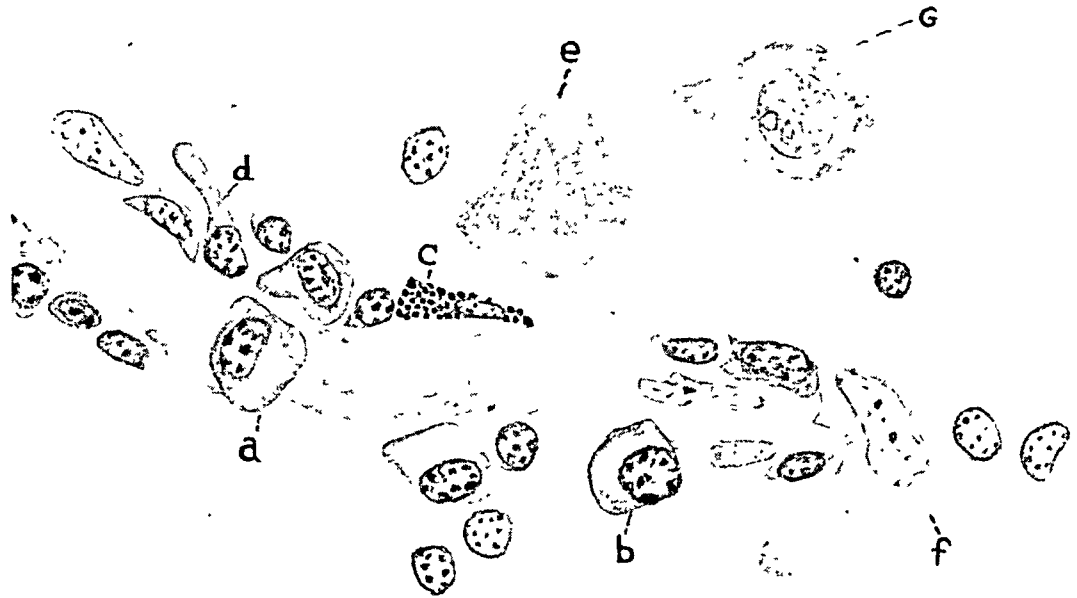


Fig. 5.—A newly formed capillary in chronic parenchymatous syphilitic encephalitis. The letter *a* indicates a plasma cell completely overlapping the capillary wall, *b* a plasma cell partly overlapping the capillary wall, *c* a plasma-mast cell, *d* a recently emigrated lymphocyte acquiring the plasma cell basophilia, *e* a degenerating glia cell, *f* a detached endothelial cell assuming the fibroblast-like structure and *g* a degenerating nerve cell.

cytoplasmic basophilia (the type lymphocyte of Marschalko), it appears that the essential changes in the differentiation of lymphocytes into plasma cells are not to be sought in an alteration of nuclear architecture alone, but also in the development of a deeper basophilia on the part of the cytoplasm. Associated with the latter is another fairly constant alteration—the formation of one or more lighter cytoplasmic areas (fig. 7) which often fuse into a continuous paranuclear zone.

The change in the basophilia of the protoplasm in small lymphocytes may be sudden (fig. 7 *a*) or gradual and synchronous with a progressive increase of cell body (fig. 7 *c*). The fully differentiated plasma cell usually has a peripheral rim

of protoplasm that stains deeper than the rest of the body cytoplasm (fig. 7 *d*). Such rims are encountered even in the smaller type of lymphocytes undergoing differentiation into plasma cells.

The large lymphocytes and large mononuclears, aside from those forming plasma cells, often change into polyblast-like structures (fig. 7 *e*) and macrophages (fig. 25 *C*). The latter contain phagocytosed pigment matter. Such macrophages are occasionally the predominant cell type of the infiltrates about small veins where they reach a depth of from one to three rows. Fully differentiated plasma cells not infrequently change into plasmamast cells, but are rarely seen to take on the character of macrophages.

It would seem that the plasma cell is a final differentiation product and not a temporary functional condition of the lymphocyte as claimed by Weidenreich and Downey, for many plasma cells are found in a process of degeneration, shown by the reduced staining affinities of the nucleus and the cytoplasm, the rarefication

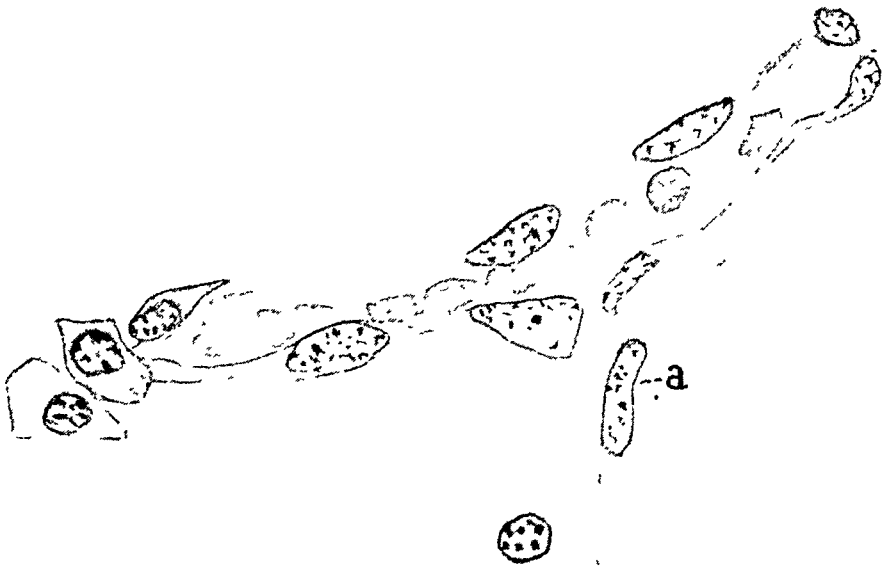


Fig. 6.—A budding newly formed blood vessel; *a* indicates free endothelial cell from an aborted capillary side sprout.

of the chromatin network and the distortion and marked vacuolization of the cytoplasm (fig. 4).

With progressive degeneration, the basophilia of the protoplasm becomes less and less pronounced, and the nuclei become pyknotic. During the degeneration of the plasma cell there frequently occurs a formation of acidophilic bodies, variously known as Russell bodies, "fuchsinophil bodies" or "hyaline bodies." They are usually of the size of an erythrocyte, but often attain giant proportions (fig. 2), most probably as the result of fusion of the smaller bodies. Thin protoplasmic strands may completely encircle the body or loop it in a horseshoe fashion. At necrobiosis, the bodies are set free in the tissue (fig. 2).

In their earlier stages, Russell bodies are represented by cytoplasmic enclosures of coarse eosinophilic granules simulating to a large extent an eosinophil type of granulation (fig. 25 *E*). They are not tissue eosinophils, for their protoplasm is deeply basophilic, while that of the eosinophils is distinctly oxyphilic. The cells

may, however, erroneously be mistaken for ripening plasmamast cells. But since the staining reaction of the Russell granules is never metachromatically basophilic but always decidedly acidophilic, we have means at hand for discrimination between the two types. The cause of the formation of Russell bodies is not known, though their frequent occurrence opens the way for speculation. The massive degeneration is not limited to plasma cells, for the entire infiltrating group, including lymphocytes, large mononuclears and plasmamast cells, often undergoes cellular alterations with the formation of pigmented cells having

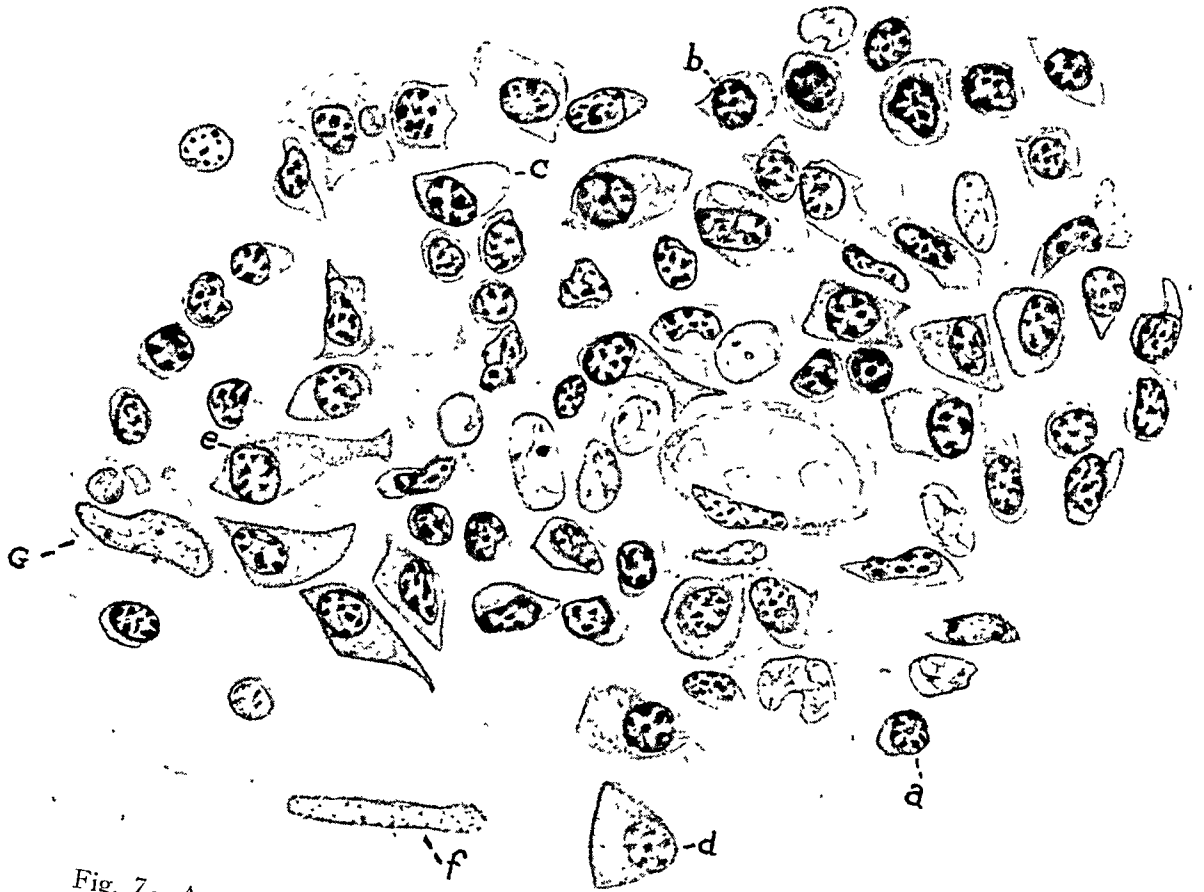


Fig. 7.—An area of intensive infiltration in chronic parenchymatous syphilitic encephalitis; *a*, *b*, *c* and *d* are lymphocytes undergoing differentiation into plasma cells; *c* is a polyblast, *f* a rod cell and *g* a detached endothelial cell.

pyknotic nuclei. The blood vessels, too, occasionally show similar regressive changes in all of their cellular components, viz., muscles, connective tissue and endothelium, with the result that the lumen of the vessels involved may become occluded with the cellular debris.

*Cells in Emigration.*—Active emigration of the infiltrating cells is frequently observed, so that it may be concluded that the vast majority of the infiltrating cells have a hemic origin. The cells in transit through the capillary wall are predominantly lymphocytes (small, medium, large) (fig. 25 C and fig. 8). The

emigrating large mononuclears, so frequently seen in poli-encephalitis, are decidedly less numerous here as an emigrating cell (fig. 25 *D*).

The changes in the outlines of both the nucleus and the cytoplasm while the cells are forcing their way through the endothelium to an extravascular habitat are extremely varied and striking. The process frequently leads to distortion of the nuclear material into deeply staining dumb-bell shape structures, or in many instances into long flagellum-like protrusions, the proximal end of which is still in the lumen, and finally may effect a more or less prolonged imprisonment of both nucleus and cytoplasm in the endothelial cell through which the emigrating cell is attempting to pass (fig. 9 *a*).

After emigration, the behavior of the lymphoid cell varies. If it is a small lymphocyte, it may immediately hypertrophy and differentiate into a plasma cell. This is most commonly the case in capillary regions, in which small lymphocytes

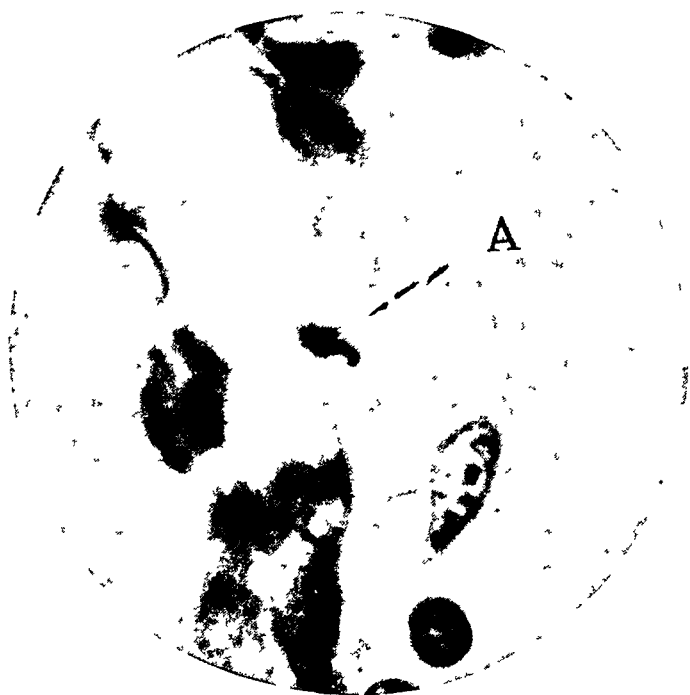


Fig. 8.—An emigrating small lymphocyte is shown at *a*;  $\times 1,500$ .

are relatively rare. In the larger infiltrations of six or more rows (figs. 2 and 7) small lymphocytes may retain their original intravascular morphology, or may hypertrophy and differentiate into plasma cells, polyblasts and even macrophages. Emigrating large mononuclears, for the most part, seemingly differentiate immediately into plasma cells or macrophages, for rarely do the infiltrations show unmodified hemic large mononuclears (monocytes). Mitosis is a frequent occurrence both in medium-sized lymphocytes and in large mononuclears.

Mitotic division in the larger plasma cells is rare. When encountered, it is nearly exclusively in the small and medium-sized lymphocytes (fig. 2 *c*). The conclusion seems warranted that mitosis ceases when differentiation into plasma cells is completed. Plasma cells are frequently binucleate (fig. 2 *e*), occasionally trinucleate and multinucleate, a condition most probably associated with the aged or functional condition (amebism) of the cell rather than indicative of amitosis, as currently claimed by von Mollendorff for the fibroblast.

*Cells in Extravascular Territory.*—The alterations in the parenchyma in extravascular territory are totally different from those observed in either poli-encephalitis or acute epidemic encephalitis. The focal infiltrations so characteristic of the last two conditions are almost entirely lacking. The nearest approximation to it are areas showing a meshlike neoformation of capillaries, in the midst of which one may find aggregations of hemic elements (lymphocytes, polyblasts and plasma cells) as shown in figure 1 *b*, but in no instance is a grouping of lymphoid cells

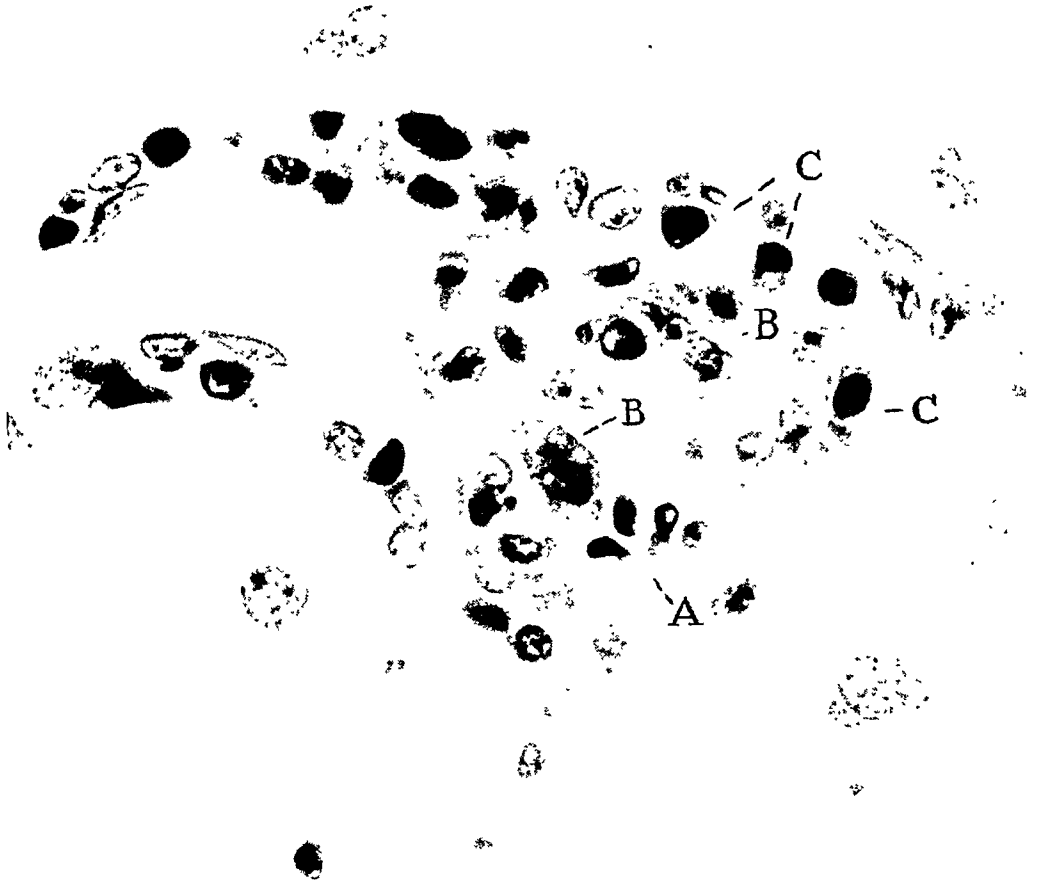


Fig. 9.—Capillary infiltration in chronic parenchymatous syphilitic encephalitis; *a* is an emigrating small lymphocyte, *b* a detached endothelial cell and *c* a plasma cell;  $\times 1,000$ .

in the form of "Taches laiteuses" observed, as seen in poli-encephalitis. A stream-like orientation and a migration of lymphoid cells away from the vessels is seldom, if ever, encountered, which explains the nonlymphoid aspect of the parenchyma in this disease (fig. 1). If the latter contains isolated, free, wandering lymphocytes, polyblasts or plasma cells, it owes their presence to single escapes, mostly from nearby capillaries. It may therefore be said that in paresis, with few exceptions, the exudate cells retain their perivascular habitat.

*Glia.*—In initial infiltrations, the glia cells frequently line up in a serial fashion parallel to the capillary, as though attempting to wall off the invading mesodermal derivatives. In the larger infiltrations, rod cells are frequently seen fulfilling the same function (fig. 7 f).

*Endothelium.*—Hypertrophy of vascular endothelium and a widespread proliferation of blood vessels of the capillary type is marked. Beginning frequently with a single, at times extremely elongated, sprout budded off from a capillary



Fig. 10—A budding capillary; *a* is a detached endothelial cell, *b* a branched capillary and *c* a detached endothelial cell;  $\times 900$ .

structure, the endothelial tube grows into the parenchyma, and undergoes further branching (fig. 10 *b*), in this way giving rise in some instances to a remarkably close meshed network of capillaries. At times, the new capillaries assume a location parallel to the parental vessels, and when they are numerous in this vicinity they give the adventitial coat of the parental vessel a honeycomb appearance. A single capillary endothelial cell or a group of such cells frequently give rise to an abortive, nonfunctioning type of capillary, thereby leaving a variable number of endothelial cells free in the parenchyma (fig. 6).



*Meninges.*—The alterations in the pia-arachnoid are marked. These consist in a decided hypertrophy of the connective tissue elements, perivascular infiltration and emigration of lymphoid cells, differentiation of lymphocytes into plasma cells and an occurrence of mast cells. Since this study is strictly limited to a consideration of the perivascular infiltrations as they occur in the parenchyma of the central nervous system, a detailed description of the pial changes is omitted.

*Comment.*—A most appropriate opportunity is therefore at hand to ascertain any possible hemohistiopoietic activity on the part of the activated endothelium. Yet, in spite of the innumerable endothelial sprouts and newly formed capillary tubes there is no evidence of a single instance in which the endothelial cells give rise to any free mononucleate exudate cells either by mitotic proliferation or by rounding up. The differences between the infiltrating elements and the endothelial cells is illustrated by the fact that while some endothelial cells in forming new capillary sprouts may become detached from the strain of endothelium that is departing from the parent vessel (fig. 10 *b* and figs. 4 and 5), they never transform into free plasma cells, polyblasts or so-called "endothelial leukocytes," but retain either their characteristic endothelial cell morphology (fig. 4 *c*) or become changed into fibroblast-like structures with typical angular cytoplasmic processes (figs. 4 *d* and 9 *b*). A transitional stage in this transformation of the endothelial cells, characterized by the initial and marked angular broadening of the protoplasm (fig. 4 *d*), is frequently seen about the abortive types of newly formed capillary sprouts. It is also met in the larger infiltrations (fig. 10 *a*). Hence, many of the stellate fibroblast-like structures appearing as isolated constituents of the infiltration (figs. 2 and 7) may be interpreted as detached endothelial cells that have assumed a fibroblast-like form, for the most part indistinguishable from that of the local syncytially arranged fibroblasts. Thus, all of the material investigated in this case leads to but one conclusion, viz., that the endothelium is in no way instrumental in the production of mononucleate exudate cells.

Von Möllendorff's contention that under inflammatory conditions the local fibroblasts, through amitotic proliferation and a rounding up, give rise to a variety of free cells (histiocytes, polyblasts, granulocytes) may be seriously questioned. Such a process apparently does not take place in general paresis. In not a single instance do the perivascular connective tissue cells or the so-called adventitial cells of Marchand (small, spindle-shaped, clasmatocyte-like structures skirt-ing vessel walls) show the alleged amitosis or rounding up. Therefore, it seems justifiable to assume that, in paresis as in poli-encephalitis and acute epidemic encephalitis, the vast majority of the exudate cells represent emigrated lymphocytes and monocytes, with a small number of homoplastic derivatives of preexistent or previously extravasated lymphoid cells.

Since polymorphonuclears (eosinophils, neutrophils) are extremely sparse, they apparently do not, as a cell group, take part in the inflammatory process. Mast cells, however, participate in the process to a considerable extent, for plasmamast cells are found frequently as isolated elements, and histogenous mast cells are often seen among the connective tissue elements of the larger vessels. Preparations of the dura mater with attached fragments of periosteal tissue show large aggregations of mast cells, usually of the histogenous type.

Extravasation of red corpuscles of such frequent occurrence as is found in poli-encephalitis and epidemic encephalitis is not noted, only a few isolated red corpuscles being present among the infiltrating cells.

Though specific stains were not employed, the hematologic technic used disclosed a decided increase of the collagenous fibers in the larger blood vessels, many of which showed progressive and regressive changes as originally outlined by Alzheimer.<sup>37</sup>

## CASE 2. CHRONIC PARENCHYMATOUS SYPHILITIC ENCEPHALITIS (PARESIS)

The striking and rather uncommon feature in chronic parenchymatous syphilitic encephalitis is the widespread and in places extensive hyalinization in the cortex, causing marked alteration in the parenchymal architecture (fig. 11).<sup>38</sup>

The hyalinization spares the molecular layer and ceases abruptly at the base of the polymorphous layer. None of it is noted in the subcortex (white matter of the brain). Whenever it occurs, notably in the region of the large pyramidal cells, it involves the cellular elements, as well as the blood vessels. It disrupts the neuroglial supporting tissue into innumerable deep-staining, ragged clumps. At times, it assumes the form of massive, homogeneous structureless deposits, which replace all the normal cellular structures. These masses often acquire a mosaic-like distribution of small, irregular, light-refracting, hyalinized solid blocks (fig. 11*a*). As a rule, glia nuclei with fragments of cell protoplasm are engulfed in the hyalinized mass, lodged in small spaces, giving the appearance of being enclosed in capsules.

The hyalinization in the blood vessels affects selectively the capillary type. Under low power, field after field shows many capillaries completely or partially hyalinized. About larger vessels, hyalinized material frequently forms collar-like masses intimately hugging the vessel wall. Constituents of the latter, especially the collagenous fibers, also undergo hyalinization. The intima of vessels so affected often splits into a series of homogeneous superimposed loops, between which there are arrested migrating cells. Frequently, the entire vessel shrinks into a solid, structureless mass, with the cellular elements either displaced to the periphery or encased in the hyalinized mass. In the latter location, the cells are frequently enclosed in a cavity of lacuna not unlike that seen in cartilage. Long stretches of small patent cylinders are met alongside of completely solidified capillary walls, which present a pattern not unlike that observed in mesenchymal bone formation and the linear marginal seriation of the osteoblasts characteristic of the latter is here simulated by the exudate cells, one or two rows of which are irregularly enmeshed or embedded in the vessel wall. Occasionally, the hyalinizing process causes a partial or complete degeneration of the enclosed cells. The latter show distortion and vacuolization of the protoplasm and pyknosis of the nuclei; however, more often, the cells retain a relatively normal morphology.

37. In giving the histologic observations in the cases of general paresis to follow, emphasis will be laid on important differences rather than on details already described.

38. In a recent paper, K. Löwenberg (*Ueber hyaline Degeneration der Grosshirnrinde bei Progressiver Paralyse*, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **93**:1, 1924) described cases of general paresis with a similar extensive hyalinization of the cortical parenchyma and blood vessels. With the aid of chemical tests, he concluded that the structure is not amyloid, and is not related to fat or calcium deposits. The phenomenon, in his opinion, is essentially the result of changed nutritional conditions, the hyalinization of the vessels (especially of the media) being primary, the alterations in the parenchyma secondary.

Nonhyalinized vessels, many of which are present, often attain a maximal infiltration of from four to five rows. The cells here are predominantly lymphocytes, but plasma cells and macrophages are also present in varying proportions. Isolated mast cells occur about as frequently as in case 1.

In direct proximity to the vessels, as well as in the more remote extravascular territory, Russell bodies are observed. They are usually found in groups of from ten to fifteen, collected into a spherical mass. They are also found in the plasma cells, but decidedly less frequently than in these cells in case 1.

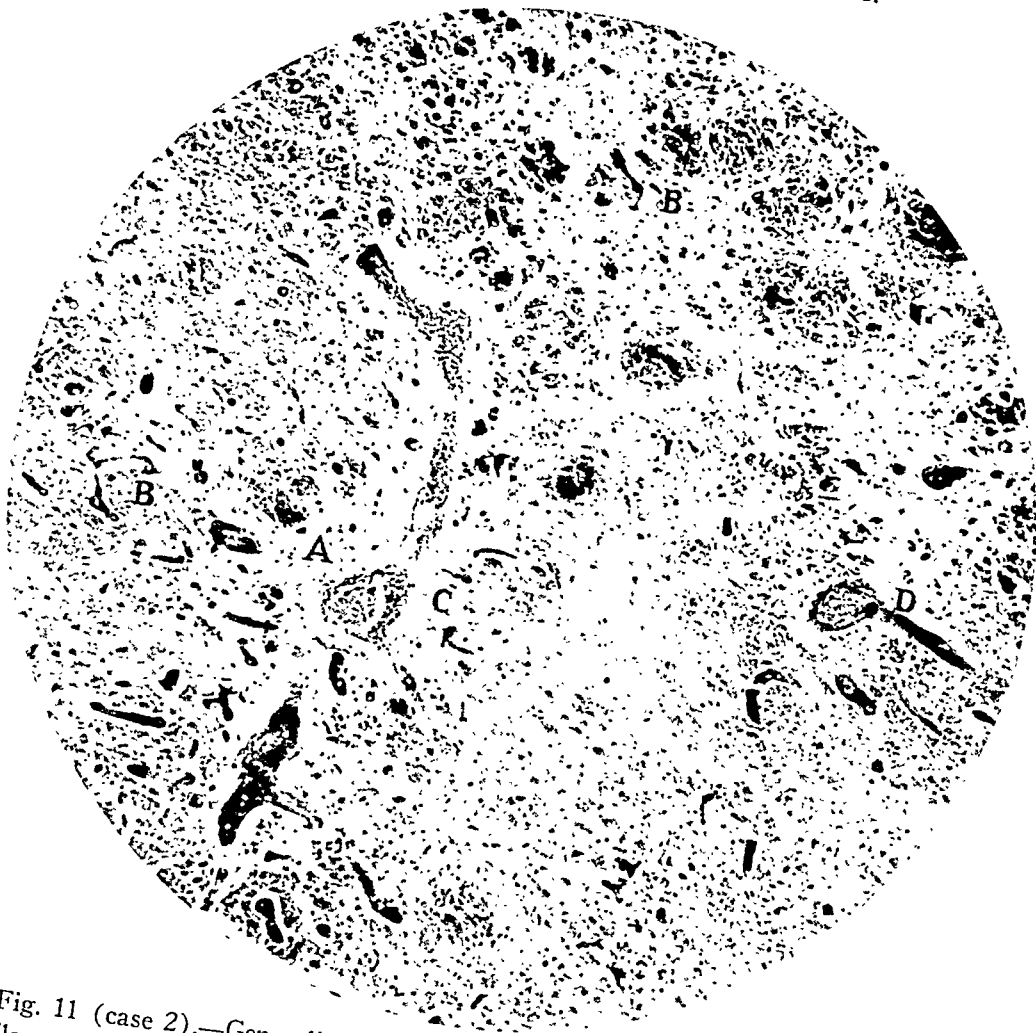


Fig. 11 (case 2).—Generalized hyalinization of capillaries in the cortex with a similar process in the parenchyma (black dots);  $\times 65$ . The letter *a* indicates mosaic-like hyalinized solid blocks, *b* a hyalinized capillary, *c* an area of infiltration and *d* a hyalinized vessel.

In the hyalinized walls of many vessels are seen lymphocytes presenting the form of emigrating cells (fig. 12). It seems probable that the hyalinizing process, setting in before the cells had time to reach an extravascular habitat, have arrested their progress and encased them in the inert, homogeneous substance. If this view is correct, it may be assumed that one is dealing here with a "fossilized" emigrating lymphoid cell. It may be regarded as additional evidence in favor of

our contention that the majority of the exudate cells are hemic in origin. In our previous paper, we stated that the emigration of hemic cells is at times slow and arduous, because the cells frequently become lodged or compressed between the endothelial cells through which they are seeking passage. The effect of the hyalinization in this case offers additional evidence of the correctness of this view.

The hemic monocytes often assume a bizarre shape in emigration. This is particularly true around nonhyalinized vessels in zones of relatively normal parenchyma. The pictures of emigration in this case are somewhat less numerous than in case 1.

Though new formation of capillaries especially in the cortical layers is extensive, not in a single instance does the endothelium or local perivascular connective tissue give rise to free wandering cells of the polyblast type. Detachment of endothelial cells from the vessel wall with subsequent transformation into fibroblast-



Fig. 12.—An emigrating large mononuclear (a) encapsulated in the hyalinizing mass;  $\times 2,000$ .

like elements is less frequent here than in case 1. This is probably due to the hyalinization of many of the vessels.

*Spinal Cord.*—Sections of the cord show a widespread new formation of capillaries, especially in the gray substance. These rarely show infiltrations.

*Meninges.*—The pia is characterized by a perivascular infiltration much more pronounced than in the previous case.

### CASE 3. CHRONIC DIFFUSE PARENCHYMATOUS SYPHILITIC ENCEPHALITIS

An outstanding feature of the condition represented in this case is the widespread and highly branched type of neocapillary formation (fig. 13). Perivascular infiltrations are decidedly less extensive here than in cases 1 and 2, with many vessels, though markedly altered, showing practically no exudates. The infiltrations about the capillaries consist, as a rule, of a single broken row of plasma cells

and lymphocytes in various stages of transition. The same is true of the infiltrations that reach the depth of from four to six rows about some of the larger vessels.

Peculiar to this case is the relatively high percentage of macrophages, which are nearly the only type of cell about some vessels while small lymphocytes predominate about other vessels, and about still others, notably the precapillary venules, plasma cells of oblong spindle contour are particularly numerous. Mast cells and plasma cells containing Russell bodies are extremely sparse here. Rod

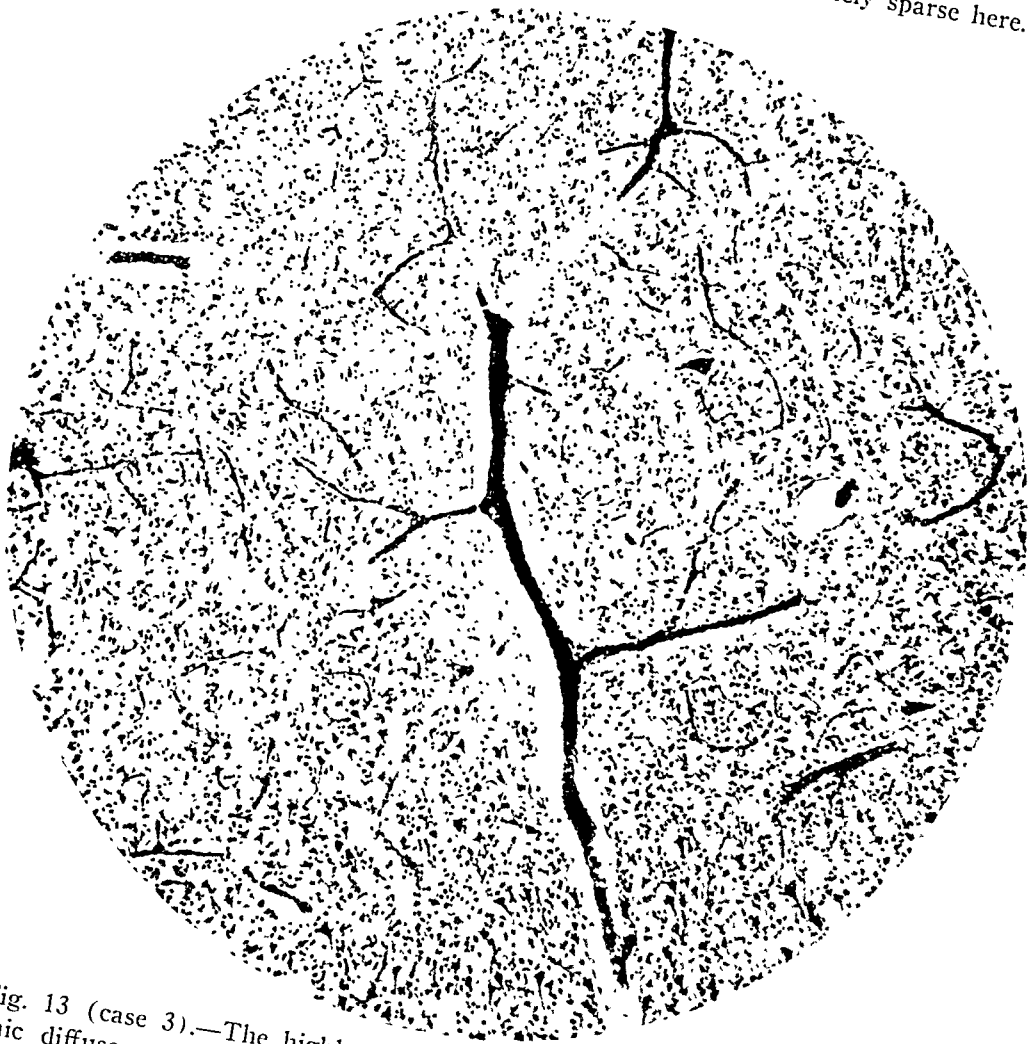


Fig. 13 (case 3).—The highly branched arborial form of new capillaries in chronic diffuse parenchymatous syphilitic encephalitis;  $\times 65$ .

cells, on the other hand, are especially numerous. Extravasation of red corpuscles is in some places as pronounced as in poli-encephalitis.

Aside from many detached endothelial cells which assume a fibroblast aspect, the vascular and capillary endothelium here again shows no evidence of producing free mononuclear phagocytic cells. This is particularly true of vessels about which macrophages constitute the major portion of the exudates, and also of the local vascular connective tissue elements. On the other hand, lymphocytes and



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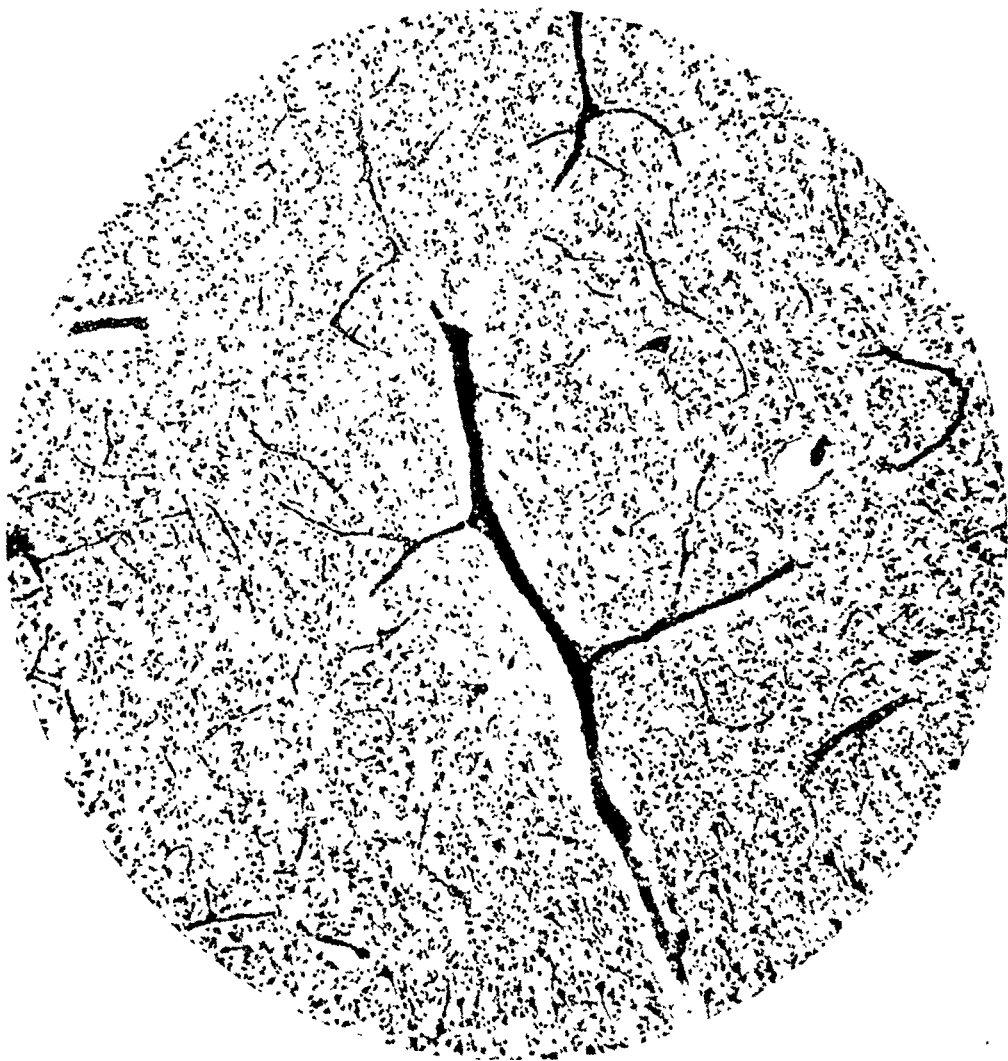


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monocytes are frequently seen in transit through the vessel wall, warranting the conclusion that in this case as in the two previous instances the vast majority of the mononucleate exudate cells are hemic in origin.

#### CASE 4. MENINGOVASCULAR SYPHILIS CEREBRI

This case shows an unusually wide distribution and a massive type of perivascular infiltration. In the midbrain and especially in the pons, some of the



Fig. 14 (case 4).—Meningovascular syphilis cerebri. The infiltration is restricted to the space of Virchow-Robin. The pia-arachnoid is thickened and thickly infiltrated;  $\times 80$ .

larger vessels show infiltrations from twenty to twenty-five cell rows in depth. The cells are so closely grouped as to give the perivascular area a block-pavement aspect (fig. 14). The vast majority of the infiltrating cells are small and medium-sized lymphocytes. Plasma cells, with intergrades from the lymphocytic types, are far less numerous than in the cases of paresis. The infiltrations often attain depths as great or even greater than those seen in poli-encephalitis, but in no instance do they show the migratory, centrifugal orientation from the vessel wall



that is shown in encephalitis. They are strikingly restricted to the adventitial habitat and this very likely accounts for the nonlymphoid aspect of the parenchyma, which, aside from a widespread new formation of capillaries, is relatively free from mesodermal elements. However, in a few locations, exudates are found extending considerable distances from the vessel wall; in such instances, the infiltrating elements represent pial derivatives invading the interior of the brain. The pial alterations with the massive infiltration by lymphocytes and plasma cells often obliterate the boundaries between meninges and nervous tissue, the advancing lymphoid mass repeatedly carrying into the interior of the brain large and heavily infiltrated vessels, which may be traced back to an equally infiltrated parental vessel in the pia. Owing to this diffuse and advancing marginal infiltration, the neuroglia tissue in such affected regions reacts with considerable activation and mobilization, often giving rise to a linear arrangement of the glia cells against the vessel wall and a formation of compound granular cells with similar perivascular orientation.

The more deeply situated and larger vessels show infiltrations averaging from four to five rows in depth, while capillaries and postcapillary venules exhibit from one to two rows of exudate cells predominantly lymphocytes, many of which show mitotic proliferation. Large mononuclears are present in varying proportions. Mast cells are extremely sparse; polymorphonuclears are nearly entirely lacking, and eosinophils are only occasionally found.

In the more extensive infiltrations there are innumerable instances of lymphocytes and large mononuclears passing through the vessel wall. Occasionally, extravasation of lymphoid cells seems to have been accomplished through definite breaks in the endothelial lining, shown by the large quantity of red cells located in the adventitial spaces and the adjoining parenchymal tissue about such vessels.

There is marked hypertrophy of the endothelial cells and an extensive new formation and budding of capillaries. The endothelium, however, is apparently not concerned with the production of large mononuclear exudate cells or the so-called endothelial leukocytes.

Sloughing off of endothelial cells is a more common occurrence here than in general paresis. The completely detached structures either retain the characteristic endothelial morphology or became transformed into fibroblast-like elements, but never into free wandering phagocytic polyblasts (fig. 15). This is particularly true of the abortive type of capillaries in which the apparently separated endothelial cells have full opportunity for a display of a possible latent cytopoietic tendency. Even here, the detached cells are never seen to round up, but acquire a characteristic irregularity of the cell body, with an oblong or oval nucleus, which is poor in chromatin content, thus becoming indistinguishable from fibroblasts.

In areas somewhat remote from blood vessels or in zones totally devoid of vascular constituents are strands of cells arranged in cords or in tubes, the nature of which is not clear (fig. 16). An endothelial origin for them was claimed by Dunlap in a recent paper on encephalitis, in which there are photomicrographs of similar structures. In our material, these cells are not seen rounding up or phagocytosing foreign material, as it was claimed by him that they did in his cases. Since occasionally these strands can be traced to the ependymal lining, they might be regarded as derivatives of ependyma invading the parenchyma.

#### CASE 5. MENINGOVASCULAR SYPHILIS CEREBRI

The perivascular infiltrations in this case are of a decidedly less pronounced character than in case 4, with the exception of areas of softening, in which they are extensive.

The pia-arachnoid membrane covering the areas of softening is a thickened mass of lymphoid cells composed mainly of densely packed lymphocytes and plasma cells, among which there are many eosinophil leukocytes. Beneath this lining, the area of softening extends inward to a great depth over the entire cortex (fig. 17).

In the area of softening there is an intensive activation and mobilization of the glia elements with the formation of free compound granular cells, which in places take the character of solid masses. The walls of the larger blood vessels show

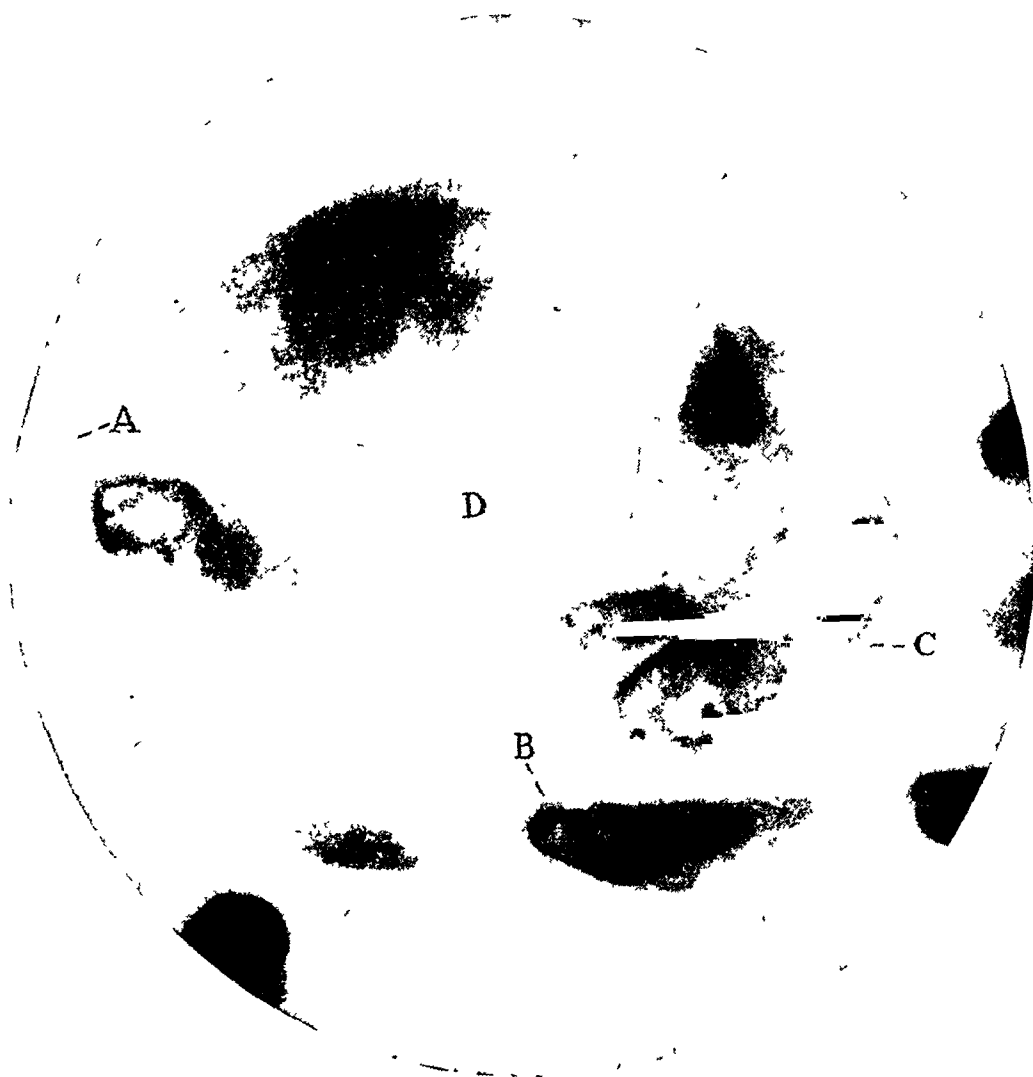


Fig. 15.—Detachment of endothelial cells; *a* indicates an initial loosening of an endothelial cell, *b* an endothelial cell retaining its normal morphology and *c* an endothelial cell undergoing transformation into a fibroblast-like structure. The lumen of the blood vessel is indicated by *d*;  $\times 3,000$ .

a varying quantity of exudate cells, predominantly lymphocytes and plasma cells. Both types of cells are frequently encountered in the extravascular territory, but, as a rule, the majority of these cells on extravasation either undergo degeneration or differentiation into compound granular cells. This is seen in the many transitional stages of lymphocytes. The process is essentially the same as that described in our previous paper on polienccephalitis, with this difference, that frequently and

especially in the newly formed capillary the hemic lymphoid cells accomplish their transformation while they are still in transit through the vessel wall or immediately thereafter. The sparsity of plasma cells in the midst of exudate cells in the extravascular territory in the area of softening may be accounted for by the rapid differentiation of the infiltrating elements into compound granular cells; typical transitional stages are not an infrequent occurrence.

Eosinophil leukocytes are in places so numerous that these places simulate fields of focal eosinophilia. Both the gitter cells and the large mononuclears

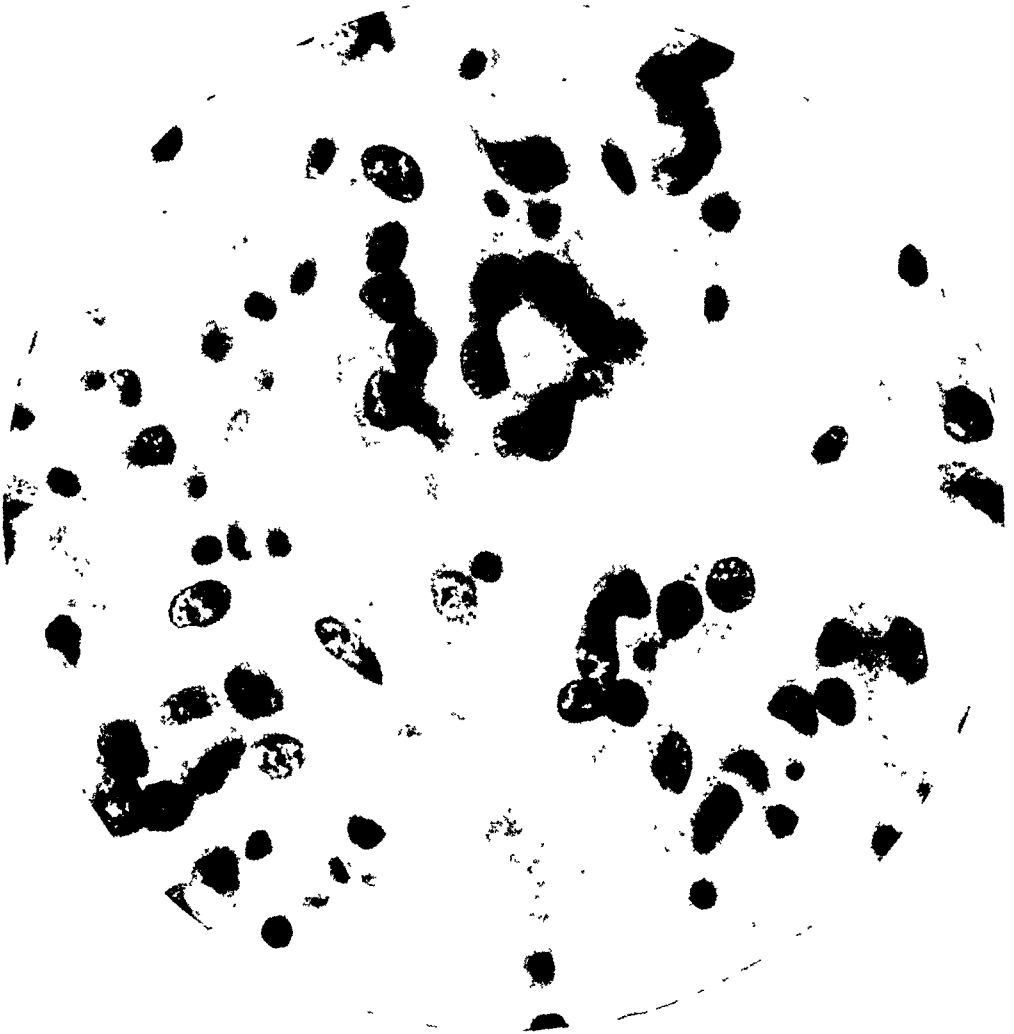


Fig. 16.—Cords and tubes of ependymal cells (it is not likely that these are endothelial cells);  $\times 900$ .

exhibit phagocytic tendencies, the engulfed material being, prevailingly, broken red corpuscles.

The zone characterized by a marked formation of new capillaries, capillary sprouts and venules ends repeatedly in a frayed out, loose aggregation of syncytially arranged cells. In close proximity to the latter there are large isolated cells with long cytoplasmic spiny processes and lightly staining nuclei, obviously instances of recently sloughed off endothelial cells. The same process may be observed in the larger vessels, demonstrating, as in no other case, the recession of endothelial cells with a subsequent transformation into fibroblast-like structures.

In the vicinity of degenerated vessels, the endothelial cells are apparently the last to become metamorphosed. The detached endothelial cells (fig. 18) either retain a characteristic endothelial-fibroblastic aspect (*a*) or become transformed into large, polymorphous, at times multinucleate structures the protoplasm of which has a ragged appearance with many long spinelike processes (*b*). None of such cells are seen differentiating into elements of the large mononuclear type. In the deeper zones of the softened cortex there is a relatively rarefied region consisting almost exclusively of compound granular cells.

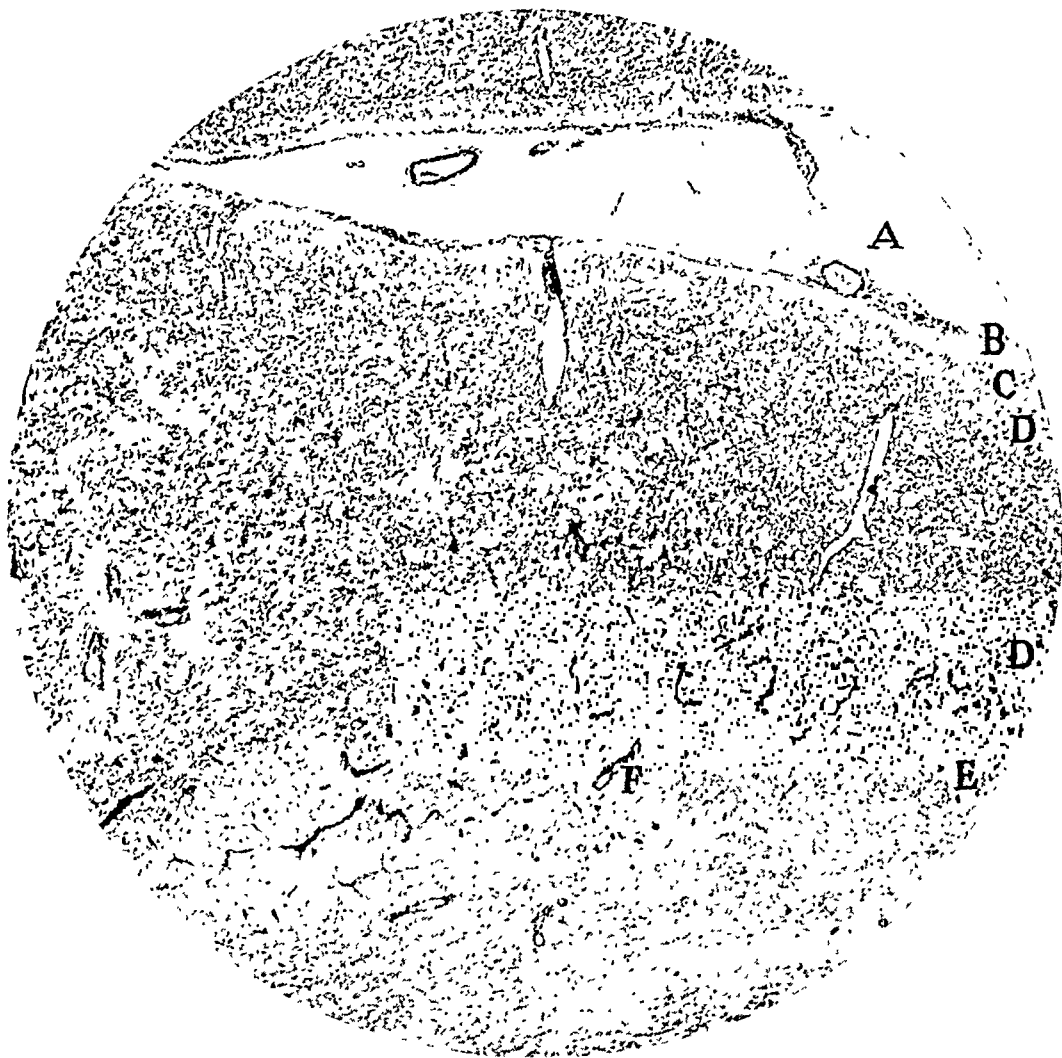


Fig. 17 (case 5).—An area of softening (from 2 to 3 mm. in depth). The letter *a* indicates the pia-arachnoid membrane, *b* the molecular layer, *c* a highly vascular layer, rich in ameboid glia cells, *d* a zone densely populated by lymphoid cells that have emigrated from the enclosed vessels, *e* degenerating blood vessels and *f* a degenerating new-formed capillary;  $\times 28$ .

In the same zone there are many degenerating capillaries showing exudates undergoing transformation into gutter cells (fig. 17 *c*). Beyond this zone there is the border line of the invading softening process. Here the neuroglia present a wide-mesh syncytial arrangement, many of the glia cells showing active ameboid movement, others presenting the various stages of a differentiation into compound

granular cells With few exceptions, practically all vessels located in this zone are in a state of degeneration. The perivascular infiltrations are represented predominantly by lymphocytes, few of which are normal

There are extensive extravasations of red cells, which are usually lodged in the adventitial spaces Still more inward there are many closely grouped newly formed capillaries with initial infiltrations (fig 17 *f*).

The softening area is particularly interesting from the standpoint of emigrating lymphocytes and monocytes Active emigration is observed in the vessels in this

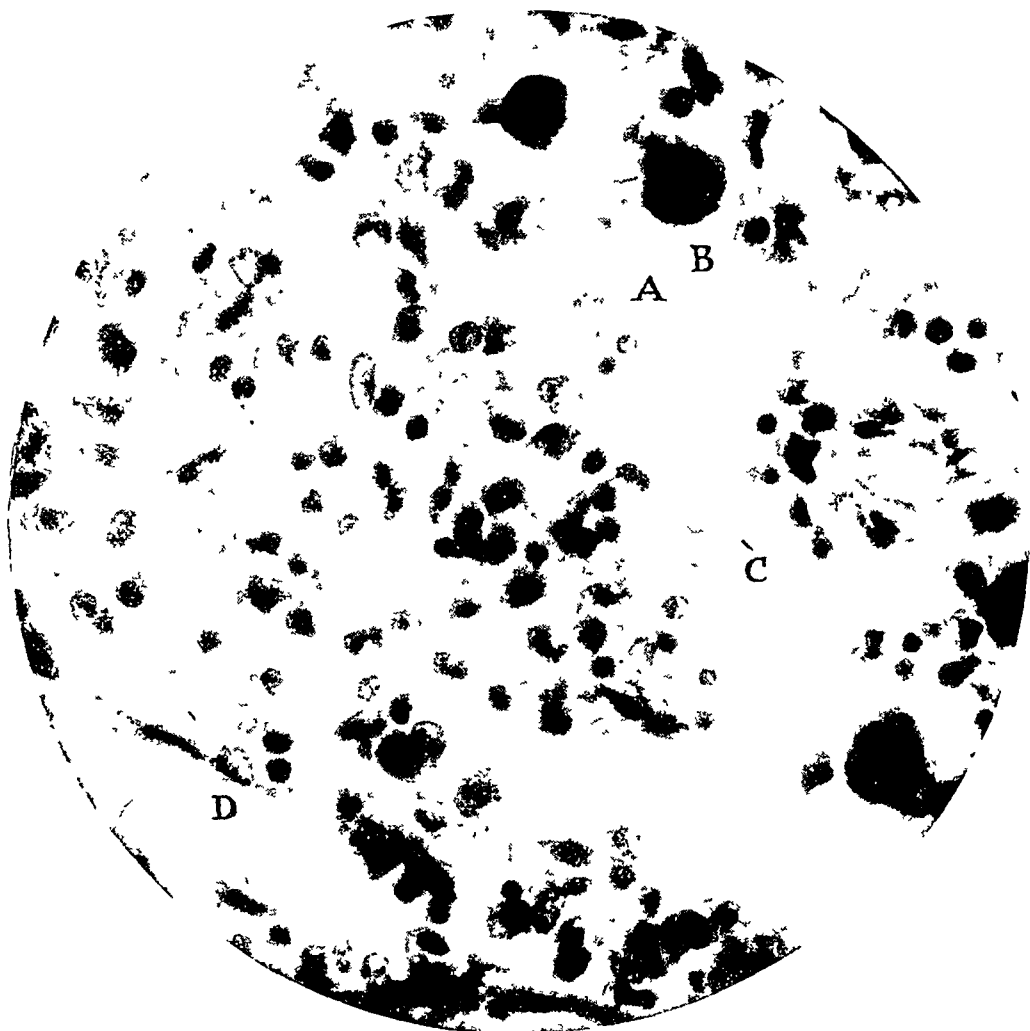


Fig. 18.—Change in zone *d* of figure 17, showing the breaking up of blood vessels, loosened endothelial cells (*a* and *b*) and gitter cells (*c*). The letter *d* indicates a blood vessel;  $\times 600$

region Emigrating eosinophil leukocytes are also seen, those in transit through the vessel wall present the same contortions of nucleus and cytoplasm as do the lymphoid cells (fig 24).

An extensive formation of new capillaries and a rebudding of the latter is also seen in the parenchymatous areas other than that undergoing softening. Groups of neocapillaries are also found in the adventitial tissue of some of the larger vessels (fig 19) in which as many as ten such structures may be counted.

In extravascular territory, the capillaries show either no exudate or few of them. On the other hand, a few of the capillaries exhibit an initial hyalinization characterized by the homogeneous, metachromatic occlusion of the lumen. Here, as in case 2, emigrating cells in isolated places are encountered showing a complete encapsulation in the hyalinized matrix. Formation of the latter is seemingly restricted to capillary regions for in postcapillary venules and in larger vessels it is never noted

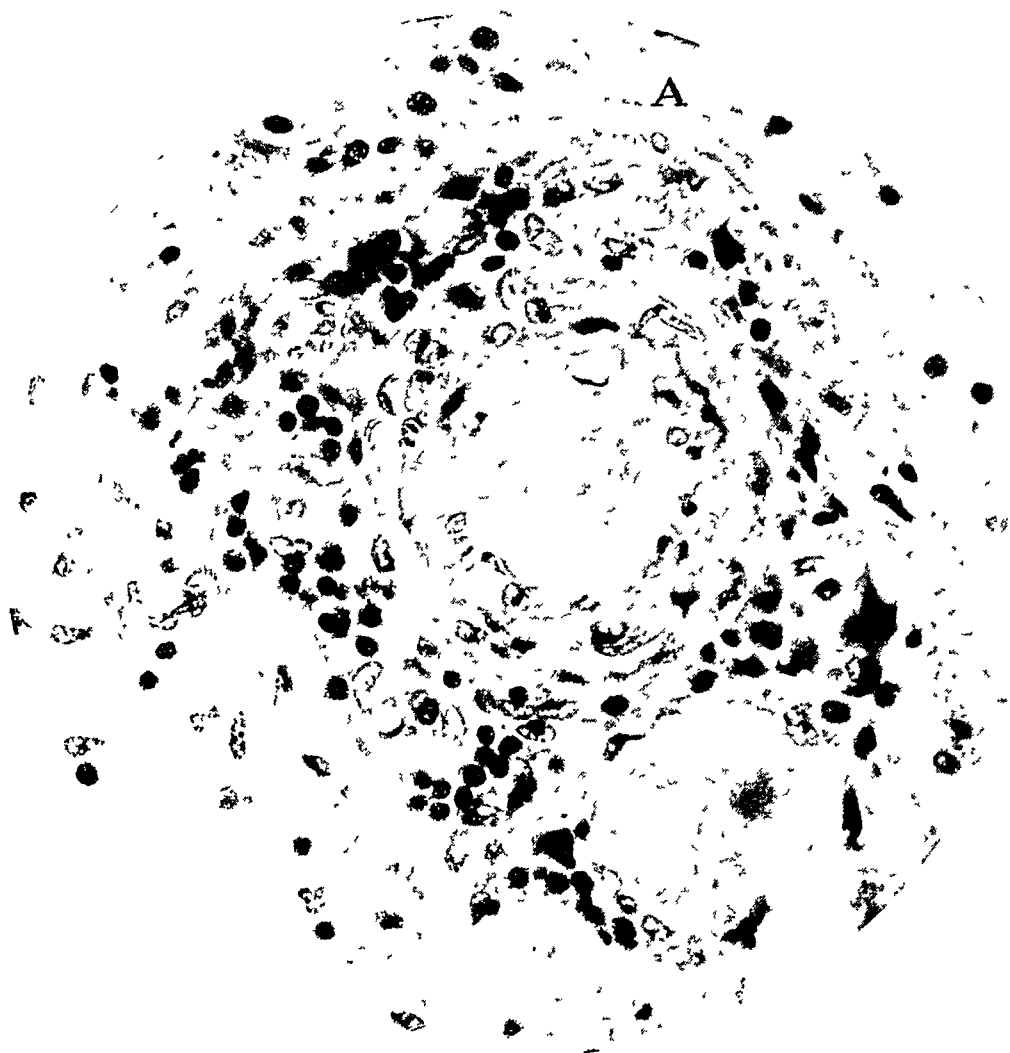


Fig. 19.—A large vessel with radially disposed new-formed capillaries; *a* indicates one of these,  $\times 500$ .

Though not as frequent as in regions of softening, the emigration encountered in other localities is nevertheless typical (fig. 20).

A sloughing off of endothelial cells with a subsequent recession from the vessel wall and the assumption of a fibroblast morphology is often noted. Aside from this, the endothelium and its adjoining perithelial connective tissue is in all instances cytogenically inactive.

#### CASE 6 MENINGOVASCULAR SYPHILIS CEREBRI

This case, unlike case 5, contains no areas of softening; still, the pial disturbances are extensive. Massive lymphocytic collections show streamlike fur-

rows of extravasated red cells (hemorrhages). In other areas, polymorphonuclear leukocytes predominate. The larger vessels are often densely muffed with lymphocytes and plasma cells and, in addition, exhibit a well advanced hyalinization.

In spite of this vast pial disturbance, the boundary line between the cortex and the meninges remains for the most part distinct. At intervals, it is broken by a massive invasion of polymorphonuclear and mononuclear elements, with lymphocytes, polyblasts, plasma cells and a varying quantity of fibroblasts.

The marginal zone of the cortex contains numerous migrating lymphocytes, polyblasts and plasma cells in various stages of differentiation. There is no extensive neoformation of capillaries with initial infiltration as noted in case 5.

As a rule, perivascular infiltration is restricted to vessels close to their points of origin from the parental vessels in the pia. They begin there with an infiltra-



Fig 20.—A large mononuclear in transit through a vessel wall;  $\times 2,000$ .

tion of from four to six rows, but as they proceed into the cortex, they show a progressive diminution of the exudates. The perivascular elements here are predominantly lymphocytes, many of which show hypertrophy and mitotic division; occasionally, plasma cells in various stages of differentiation outnumber the lymphocytes. Large mononuclears are relatively sparse; eosinophil leukocytes and mast cells are entirely lacking or extremely rare.

The endothelium, aside from showing detachment of individual cells that frequently become indistinguishable from adjacent fibroblasts, is inactive.

The parenchyma of the subcortex is decidedly nonlymphoid, save for a few foci of infiltration, which in the midst of the highly ameboid glia cells show a varying quantity of migrating lymphocytes, histiocytes and polyblasts. The perivascular infiltration is slight. In maximal proportion, it reaches from three to four rows in some of the larger vessels, averages from one to two rows in many others and about capillaries is, for the most part, entirely lacking.

The lumen of some of the vessels with macrophages as the dominating infiltrate is densely populated with large pigmented mononuclears. The extravasation of

red cells occasionally met about capillaries assumes marked proportions in the adventitial spaces of a few of the larger vessels.

New formation of capillaries is rather generalized but is not as pronounced as in the previous case. A less marked form of hyalinization is noted in some of the capillaries; it offers an opportunity for an establishment of what we propose to call "fossilized emigrating lymphocytes," i. e., cells embedded in the hyaline matrix while in transit through the vessel wall, two of which are shown in figure 21.



Fig. 21.—A hyalinizing blood vessel showing two emigrating lymphocytes encapsulated in the hyalinized matrix, "fossilized emigrating lymphocytes."

#### CASE 7 VASCULAR SYPHILIS CEREBRI

This case differs from the two that have been described in presenting relatively normal meninges. Neither infiltrating elements nor an unusual thickening is noted. The parenchyma of the brain shows a unique type of vascular lesion not seen in either encephalitis or in the various cases of cerebral syphilis described. Nearly all the larger vessels show hyperplasia of all their layers, notably of the intima. With few exceptions, such vessels show broad adventitial coats, the fixed cells of which fray out extensively into a mesenchyma-like, syncytially arranged connective



tissue network, the meshes of which are conspicuously numerous and widened. Here, in addition to the many newly formed capillaries, distinct small arteries and veins may be seen with thickened intima.

The infiltration about such vessels is nearly exclusively restricted to the adventitial coat and is composed mainly of scattered small lymphocytes, many of which have deep staining and at times decidedly pyknotic nuclei. This and the fact that plasma cells are conspicuously absent and macrophages and large mononuclears only occasionally met seemed to indicate that the infiltration had been arrested



Fig. 22.—The bizarre shape assumed by a large mononuclear in the process of emigration;  $\times 2,000$ .

in its early stages. The total lack of mitotic figures in the lymphoid exudates, the extreme sparsity of active emigrations and the nonhypertrophied and in instances pyknotic condition of the vascular and neocapillary endothelium lend additional evidence to this view.

In regions in which the neuroglia tissue has become extremely rarefied, regressive changes in the larger vessels are still more pronounced. Here the exudates are extremely sparse. The adventitial coat consists of a disorganized mass of loosely concerted connective tissue cells, many of which show signs of degeneration, a process equally notable in the disintegrating local neocapillaries. In such

vessels, little is left of the media and the intima save a distorted convoluted cellular mass, in the midst of which most prominent is the corrugated elastic membrane.

This case presents a third type of vessel, which in cross-sections simulates a large lymphatic. These vessels are composed nearly exclusively of endothelial cells, relatively few of which are normal. About such structures, exudates are, as a rule, entirely lacking; when present, they exhibit marked degeneration. These vessels are undoubtedly instances of newly formed capillaries, which subsequently have assumed giant proportions.



Fig. 23.—The dumb-bell shape of a large mononuclear in transit through the vessel wall;  $\times 2,000$

Finally, an infiltration of closely grouped cells approximating in type that in the previous cases is met with in some of the small veins and postcapillary venules. Here the exudates, while predominantly composed of small and, for the most part, normal appearing lymphocytes, included plasma cells, large mononuclears and macrophages in varying proportions. A few active emigrations are encountered. Sloughed off endothelial cells with a retained irregularity of cytoplasmic contour are likewise encountered, a phenomenon not noted in the previously described vessels

Occasionally, larger vessels running in from the periphery are accompanied by connective tissue septums, which at intervals are densely populated by long, spindle-shaped, clasmatocyte-like structures heavily laden with greenish pigment granules. The latter are found in local macrophages and in the fixed endothelium. In spite of this, however, no genetic relationship can be established between the pigmented free cells and the vascular endothelium. On all occasions, the endothelium, as well as the perithelial connective tissue, is cytogenically inactive in respect to a production of the so-called endothelial leukocytes or large mononucleate exudate cells.

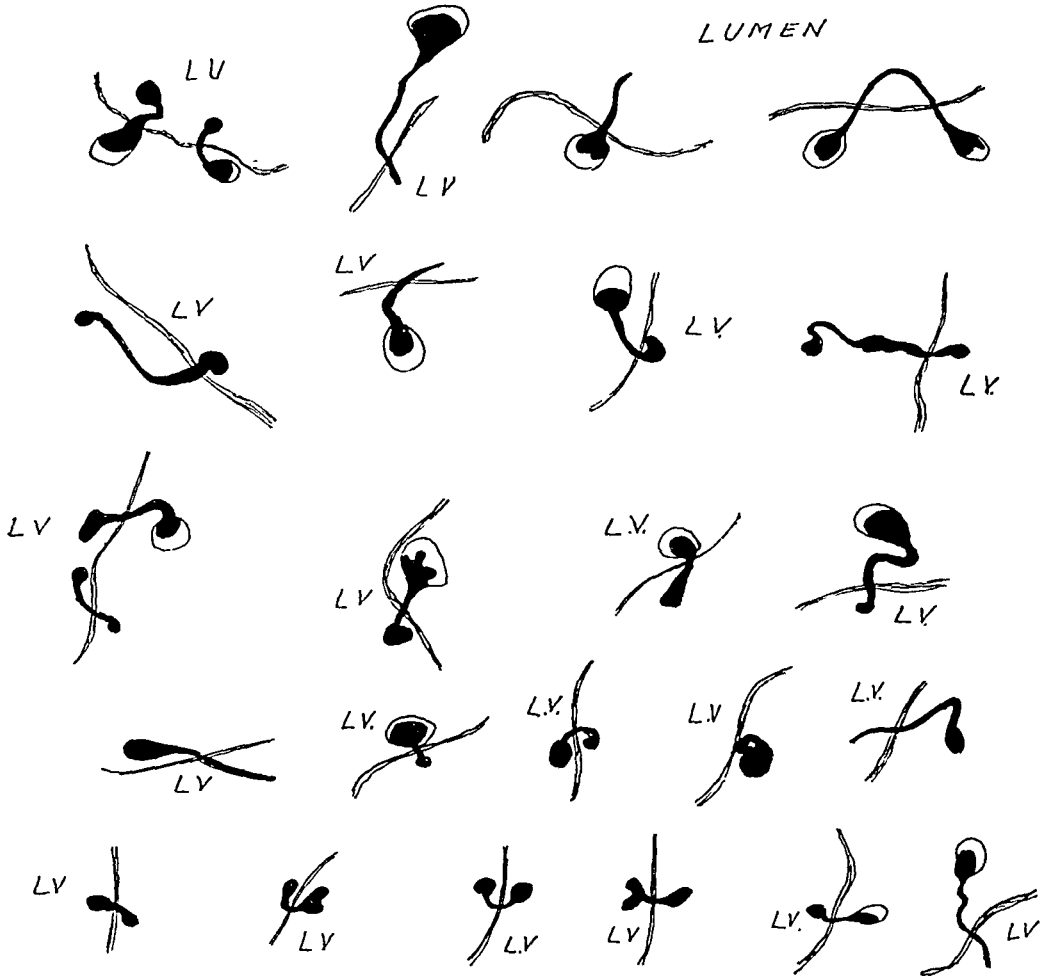


Fig. 24.—Various alterations in contour of nucleus and cytoplasm assumed by lymphoid cells during emigration: the upper three rows are large mononuclears; the lower two rows are small and medium-sized lymphocytes. *LV* designates the vessel.

All the figures were drawn with the camera lucida at a uniform magnification. Leitz apochromatic oil immersion  $\frac{1}{12}$  Fl. objective; compensatory oculars  $\times 10$ .

#### SUMMARY

Beginning with the earliest investigations of Cohnheim and his contemporary Virchow, the nature, origin and significance of the so-called small round cell infiltration occurring in various inflammatory conditions have been the subject of repeated investigations and discussion. The

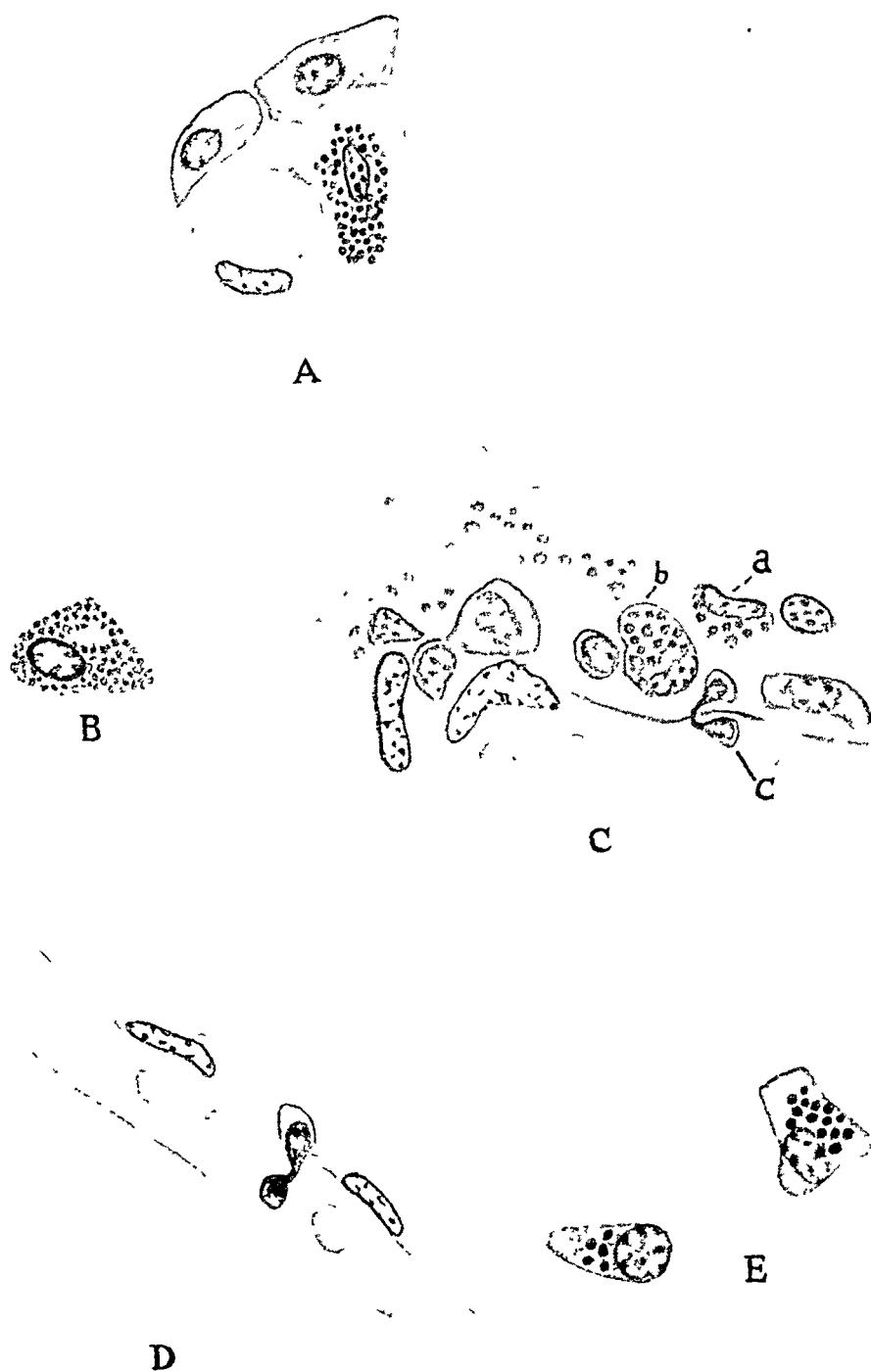


Fig 25.—*A* shows an initial infiltration about a capillary, showing a plasma-mast cell and two plasma cells; *B*, a typical plasma cell displaying the paranuclear clear area; *C*, a lymphocyte (*a*) and a large mononuclear (*b*) acquiring the character of macrophages, (*c*) an emigrating lymphocyte; *D*, an emigrating large mononuclear; *E*, Russell bodies simulating eosinophil granules enclosed in plasma cells.



literature claiming a histogenous origin for these cells, though decidedly more extensive than that arguing for a hemic origin, is, however, by no means equally conclusive.

Ranvier established the existence of a free wandering type of cell in the loose connective tissue (clasmatocytes) that under normal and pathologic conditions exhibits polyvalent hemohistiopoietic potencies. This was verified by subsequent workers, who variously named these structures resting wandering cells (Maximow), adventitial cells (Marchand), histiocytes (Kiyono) and hemohistioblasts (Ferrata). These cells were investigated from the point of view of embryogenesis and comparative histogenesis and were recognized in natural and experimentally produced inflammatory conditions. Their character was determined by intra vitam staining with various colloidal dye injections (Pyrrholblau, trypanblau, lithium-carmin), by growth of various tissues in vitro and by the supravital staining methods (neutral red, Janus green). It was then found that these variously named, dye-storing cells belong to the coherent organization that in current literature has definitely become recognized as the histiocytic apparatus or the reticulo-endothelial system.

It is now a well established fact that in the adult organism there are, in addition to the generalized resting wandering cells, fixed histiocytic elements that under normal and especially under pathologic conditions may mobilize, proliferate and round up to form free wandering phagocytic elements, including granulocytes. These fixed histiocytic cells constitute the reticular cells of the lymphoid and myeloid tissue, the cells lining the sinuses of the lymph nodes and the venous channels of the bone-marrow, spleen and liver (Kupffer cells) and possibly the cells lining the venous capillaries of the suprarenal glands and the hypophysis. It is this group of cells only that is correctly covered by the term reticulo-endothelium. In this restricted sense, the term is particularly appropriate, reticular implying the histologic character of the riporinal cells; endothelium their function in establishing channels for the lymph and the blood stream through the respective organs.

No sooner had Goldman,<sup>39</sup> Tschaschin,<sup>40</sup> Aschoff and Kiyono,<sup>41</sup> Kiyono<sup>42</sup> and others established the morphology and cytopoietic signifi-

39. Goldman, E. F.: I. Die äussere und innere Sekretion des gesunden und kranken Organisms im Lichte der vitalen Färbung, Beitr. z. klin. Chir. **64**:192, 1909; II. **78**:1, 1912.

40. Tschaschin, S.: Ueber die ruhenden Wanderzellen und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphocyten, Folia haemat. **17**:317, 1913.

41. Aschoff, L., and Kiyono, K.: Zur Frage der grossen Mononukleären, Folia haemat. **15**:383, 1913.

42. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

cance of the reticulo-endothelial system than repeated attempts were made to include the generalized vascular endothelium (both deep seated and peripheral) as actively participating in the production of the free wandering phagocytic cells. In the current literature, such vascular endothelial derivatives are spoken of as endothelial leukocytes (Mallory, 1914), large mononuclear phagocytes (McJunkin, 1925), endothelial phagocytes (Foot, 1925) and monocytoïd elements (Di Guglielmo, 1926).

Pathologists, especially, are prone to adopt this view of a vascular endothelial origin of the large mononuclear to account for the frequent appearance of this type of cell in a variety of infectious diseases, such as malaria, endocarditis lenta, streptococcemia, tuberculosis, syphilis and various other types of chronic inflammatory lesions. This tendency may be traced to Patella (1903-1923), who regarded large mononuclears and the major portion of the lymphocytes as "cadaverously" isolated vascular endothelial cells. It was substantially influenced by Mallory (1898) with his repeated assertion (1914) of a vascular endothelial origin for the endothelial leukocytes, and is seemingly difficult to dis-establish because of Marchand's (1898-1902) classical studies on the polyvalent cytopoietic potencies of the adventitial cells skirting the blood vessels. Influenced by the investigations of his pupil Herzog, Marchand in recent years (1921-1924) considered the adventitial cells as derivatives of the vascular endothelium, which, when in a free ameboid state, are capable of giving origin to many of the small elements appearing in inflammatory lesions.

Indeed, it is proved that endothelial components of the reticulo-endothelial system exhibit polyvalent hemohistiopoietic potencies under normal and especially abnormal conditions, but attempts to prove a similar potency for the generalized vascular endothelium have thus far been strikingly inconclusive. In spite of the numerous investigations made and the various methods employed (especially that of injections of india ink) the evidence to date has not been sufficient to justify the axiomatic conclusion that the generalized vascular endothelium gives origin in any notable quantity to macrophages, polyblasts, small and large mononuclears, histiocytes, epithelioid cells, dust cells, syncytial or giant cells, or any of the free wandering cells met in inflammatory reactions. The situation is admittedly different in respect to the reticulo-endothelial system, for here any of the aforementioned cells may differentiate from the local endothelium, which, to avoid an all too prevalent confusion, might be called the riporinal endothelium as contrasted with the vascular endothelium.

That even monocytes take their origin from the reticulo-endothelial system has repeatedly been asserted (Schilling, Schittenhelm and Erhardt, Masugi, Buengler and others). This view, disparaged by the

late Maximow, has recently been categorically denied by Bloom, who maintains that proof of such a transformation is lacking.

The present investigation, like the previous one on encephalitis, afforded ample opportunity for a detailed study of the cytopoietic powers of the vascular endothelium. The reactive phenomena of the latter were noted under a variety of conditions, such as hypertrophy, swelling, new formation of capillaries, disintegration of constituent cells, partial or total degeneration and breaks in vessel walls because of massive diapedesis, yet no instance was recorded of vascular endothelium participating in any way in the production of free wandering cells (large mononuclears, histiocytes, polyblasts, macrophages) either through mitotic proliferation, desquamation or otherwise.

In syphilitic lesions, endothelial cells frequently become sloughed off from the vessel wall, but such detached cells either retain their characteristic endothelial aspect or become transformed into fibroblast-like structures, which, when somewhat receded from the vessel wall, are frequently indistinguishable from adjoining perivascular fibroblasts. This observation is by no means new. Over a quarter of a century ago, Maximow recorded the phenomenon as occurring in inflammatory reactions and has subsequently rediscovered the process in variously treated tissue cultures.

Important recent corroboration of the desquamation is found in the observations of Clarke and Clarke (1927) in living capillaries of amphibian larvae. The detached endothelial cells, in their opinion, remain specific and are devoid of ameboid movement. The phenomenon, in their opinion, is due to a weakened condition of the animal or to some mechanical injury.

Jolly in his earliest works, by means of injections of silver nitrate into the peritoneal cavity, observed the similar phenomenon of a sloughing off of endothelial cells and observed that, on occasions, "*les cellules endotheliales ont pris l'aspect de veritable cellules conjonctives*" (the endothelial cells appeared like true connective tissue cells). Jolly (1923) differed with Maximow by asserting that while some of the endothelial cells are altered in this fashion a considerable quota of them become rounded up into spherical structures (macrophages, polyblasts).

For the most part, contemporary workers on endotheliopoiesis, Herzog, Marchand, Dunlap, Oeller, Töppich, Siegmund, Sabin, Doan and Cunningham, Di Guglielmo, Foot and others, failed to mention this recession from the vessel wall of endothelial cells that retain the endothelial morphology or assume a fibroblast-like appearance. Histogenically, the process should offer no difficulty, since embryologically the early endothelial cells represent modified mesenchymal cells; the occurrence of a reverse process under pathologic conditions in which endothelial cells assume a fibroblast-like morphology may readily be conceded.



In current contributions on the origin of the perivascular exudates, the vague statement is often made that they arise from the cells of the vessel wall or from the so-called "Gefäßwandzellen." Since both expressions leave one in a quandary as to what type of cell is meant, their use should be discontinued, especially so since in the light of modern hematology a sufficient variety of terms is available to describe accurately the various types of cells that may be encountered in the vessel wall.

A step in this direction is taken by von Möllendorff, who in his recent work interpreted the adventitial cells not as independent specific entities but as attached constituents of the general fixed fibroblast-net. His views as to the polyvalent hemohistiopoietic potencies of the fibroblast need not be discussed at length here; it is only necessary to say that the specificity of the fibroblasts is so well established that a resuscitation of older theories assigning a developmental capacity to the cell will occasion only needless discussions.

Over twenty-five years ago, Maximow (1902) contributed his classical studies on the inflammatory reaction of the connective tissue elements, notably that of the fibroblasts. In this work, he showed that the fibroblasts had a specific spindle-shaped stellate form, that their only mode of proliferation was through mitosis, and that among the various other inflammatory cells they played a decidedly unimportant rôle. This view Maximow subsequently corroborated by observation on cultures of connective tissue; for here, in the living condition, fibroblasts likewise appeared as specifically established elements with no evidence of further progressive histogenetic powers. Finally, in his last studies<sup>43</sup> on explanted tissues, he was able to show that lymphocytes may develop into fibroblasts, which, once established, notably never lose their specific morphology but, in laying down typical connective tissue, assume the function of ordinary fibroblasts.

Identical results were obtained by Bloom (1928). Rabbit lymph cultures in vitro showed within from six to eight hours a differentiation of small and large lymphocytes into the typical dye-storing mononuclears and polyblasts of inflammation, some of which later changed into fibroblasts.

Ferrata and the Italian school also repeatedly held out for the specificity of the fibroblasts. Jolly, admitting a phagocytic activity for the cells, regarded their final differentiation as permanent. In our own material (that on which this paper is based, as well as that on which our previous publication on encephalitis was based), the fibroblasts failed to reveal any activity in the production of free wandering cells or granulocytes, as asserted by von Möllendorff. In all instances, even when the

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43. Maximow, A.: Development of Nongranular Leucocytes (Lymphocytes and Monocytes) into Polyblasts (Macrophages) and Fibroblasts in Vitro, *Proc. Soc. Exper. Biol. & Med.* **24**:570, 1927.

perivascular infiltration was maximal, fibroblasts retained their stereotyped morphology and played a decidedly secondary rôle. When hypertrophied connective tissue was met with in its most extreme form, as for example in the semilunar ganglion in one of the cases described here, fibroblasts never exhibited the alleged amitosis as an accompanying process in the production of free cells (von Möllendorff). Binucleate fibroblasts were encountered, but these represented indentations and segmentations of nuclear material rather than direct cell divisions, for never was an interruption of protoplasmic wall or a rounding up of these cells noted. The mitotic figures were seen in fibroblasts. Those encountered seemed sufficiently typical to substantiate Maximow's recent statement that "the only conclusively demonstrated mode of proliferation of the fibroblasts is mitosis."

It is a peculiar coincidence that both here and abroad pathologists during the last twenty years have made repeated attempts to derive the large exudative mononuclears from the vascular endothelium rather than concede a direct hemic origin of the cell by way of emigration through the vessel wall. Many consider the small circulating lymphocyte a cell type as permanently differentiated as the erythrocyte (Ferrata). Hirschfeld<sup>44</sup> denied its power for progressive development in cultures of leukemic blood. Others, while admitting a diapedesis of lymphoid cells, deny or at least question the ability of these to develop into granulated elements or into polyblasts in inflammatory reactions, especially those of the acute type.

Opposed to this somewhat arbitrary stand, following the lead of the pioneers Metchnikoff, Cohnheim and especially Maximow, there is a formidable array of workers offering evidence not only of the possibility, but of the decided frequency of the emigration of lymphocytes and large mononuclears and their subsequent polyblastic differentiation. Maximow as early as 1902, in his studies on experimental aseptic inflammations, advanced his theory of a mixed origin of the exudates, maintaining that while a small quota represent derivatives of local pre-existent small wandering cells (emigrated lymphocytes) and clasmatoocytes, the vast majority are to be interpreted as hemic lymphocytes that through emigration have attained a perivascular habitat, where a polyblastic differentiation of them frequently occurs. Maximow has, in the face of strong opposition, consistently held the same opinion in his works on purulent inflammations, on the ontogenesis of blood cells, on the nature of connective tissue and recently on the cultures of lymphoid tissue, normal and inoculated with tubercle bacilli.

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44. Hirschfeld, H.: Züchtungsversuche mit leukaemischem Blut, *Folia haemat.* 34:39, 1927.

Jolly is as affirmative as was Maximow, maintaining that the major portion of the cells in inflammation is constituted of emigrated lymphocytes through diapedesis. This phenomenon of lymphoid cells passing through the cell wall has repeatedly been confirmed by various workers. A list given by Maximow in a recent review on mesenchymal reactions includes the names of Ziegler, Schwarz, Helly, Zieler, Verebély, Fischer, Homén, von Fieandt, Wallgren, Tschaschin, Bergel, Dantschakoff and Seidlein, Kraft, Stilwell, Lang and Alfejew. To this list should be added the recent work of Bloom (1928), who maintained that in subcutaneous abscesses of rabbits infected with *Bacillus monocytogenes* the exudate cells represent, exclusively, transformed emigrated lymphocytes and monocytes.

Our present studies on syphilitic lesions and those previously reported on encephalitis have revealed many instances of lymphocytes and large mononuclears (monocytes) passing through the endothelial wall in full corroboration of Maximow's and Jolly's original contentions.

In the process of emigration, lymphocytes and large mononuclears often show decided variations in their nuclear and cytoplasmic contours, but at times extravasation is accomplished with slight changes in cell area and morphology. Often both cytoplasm and nucleus are drawn out into long, irregular structures, the advancing portion of the cell containing the main mass of the cell contents. Small and medium-sized lymphocytes in transit through the capillary wall assume such a degree of basophilia as frequently to obscure all traces of cytoplasm. Hence dark, round masses with pronounced pseudopods ending in rotund fashion in juxtaposition or in contact with the endothelium are to be interpreted as emigrating lymphocytes and not as tangential sections of endothelial cells (Marcora<sup>45</sup>). Such transient lymphocytes can be seen in small capillary tubes showing perfect unbroken endothelium near which are to be found previously extravasated, migrating and dividing free cells.

Curved dumb-bell-shaped, deeply staining nuclei with clearcut cytoplasmic contours, seen frequently outside the vascular endothelium, are not desquamated endothelial cells, but recently emigrated lymphocytes or large mononuclears. Thin strands of nuclear material running from the capillary lumen to a main cell body located in the third or fifth row of lymphocytes indicate clearly that the emigration is at times slow and arduous.

After extravasation, the behavior of the lymphoid cells varies. Hypertrophy is common for all the lymphocytes. Many of the latter, together with the large mononuclears, change into polyblasts,

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45. Marcora, F.: Sull' origine delle infiltrazioni perivasali nella encefalomyelitis epidemica, *Haematologica* 2:323, 1921.

macrophages, histiocytes and plasma cells, with the differentiation into plasma cells being of far greater frequency in the lesions of syphilis than in those of poliomyelitis or acute epidemic encephalitis.

The streamlike orientation and migration of lymphoid cells in the vicinity of blood vessels so frequently noted in encephalitis gives additional evidence of a hemic origin of the cells. In the present material, this phenomenon of migrating away from the adventitial spaces was not noted, which is characteristic for infiltrations in syphilis cerebri.

To meet the question whether the active emigration does not represent superimposed cells, it may be said that this could not be the case; for all the photomicrographs portraying emigrating cells were taken with high aperture lenses and critical illumination, so that only a single plane was in focus at one time. In every instance, it was possible to choose a plane either above or below that of the depicted emigrating lymphocyte, and the conclusion seems obvious that the cell in question represented an individual lodged between the endothelial cells, through which it was seeking passage to a perivascular habitat.

#### CONCLUSIONS

In all types of syphilitic lesions, the vast majority of the infiltration elements in the adventitial spaces is constituted of emigrated lymphocytes and monocytes, as evidenced by the numerous emigration pictures seen, with a small quota of homoplastic differentiation products of preexistent or previously extravasated lymphoid cells.

As a rule, the perivascular infiltrations in the various types of syphilis are decidedly less marked than in poliomyelitis or in acute epidemic encephalitis. In one case, however, it not only equals, but surpasses that of the latter. Streamlike orientation and migration of lymphoid cells in the vicinity of blood vessels so characteristic in encephalitis is lacking in syphilis.

Among the exudates, the large mononuclear, hyperplastic and polyblastic differentiations of lymphocytes are decidedly less frequent in syphilis cerebri than in encephalitis. Macrophages only are found in the same proportion.

The described syphilitic lesions in the brain show a high ratio of plasma cells and a marked frequency of mast cells, both of the plasma-mast cell type and of the histogenous variety. The greatest number of the plasma cells is encountered in paresis, in which, in the larger infiltrations, they constitute approximately one half of the exudate.

The plasma cells represent the terminal differentiation stage of lymphocytes and monocytes; they may, however, further differentiate into plasmamast cells, as originally outlined by Krompecher.

Associated with the degeneration of the plasma cells is the formation of Russell bodies (hyaline bodies) which at necrobiosis of the cell become

freely dispersed in the tissue. The Russell bodies are always conspicuously acidophilic. They vary in size from small eosinophil, granule-like structures to giant spheres of monocytic proportions.

In no way does the vascular or the newly formed capillary endothelium give rise to free wandering phagocytic cells. A detachment of the endothelial cells occurs frequently, but such cells either retain their characteristic endothelial aspect or become transformed into structures indistinguishable from fibroblasts, especially when somewhat receded from the vessel wall.

A heteroplastic formation of exudates from the so-called adventitial cells of Marchand or any other fixed connective tissue cells and amitosis in these cells are not noted.

Extravasation of red corpuscles into the adventitial spaces occurs rarely in syphilis, but in areas of softening, it may be massive.

Polymorphonuclear and eosinophil leukocytes play practically no rôle in this inflammatory process. The latter, however, are extremely numerous in areas of softening.

The formation of compound granular cells occurs occasionally about vessels; it is exceedingly marked in areas of softening in which emigrated lymphocytes may become transformed into gitter cells.

One case presents a widespread and marked hyalinization of parenchyma and blood vessels, especially of the capillary type. In two other cases, a mild (perhaps initial) process of hyalinization is noted about some of the capillaries.

Emigrating lymphocytes and monocytes are seen embedded in the hyaline matrix; because of this fact, they may well be termed "fossilized lymphoid cells."

# IMMUNE CELLULAR REACTIONS IN EXPERIMENTAL ACUTE PERITONITIS\*

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In a previous publication, it was demonstrated<sup>1</sup> that immunization with living colon bacilli prevents a fatal outcome in fecal peritonitis. No experimental evidence was offered to explain this immunity. It had been shown earlier that immunization with colon bacilli averts death in peritonitis due to *Bacillus coli* in gum tragacanth;<sup>2</sup> it is conceivable that the survival in this type of peritonitis is due to the production of specific antibodies. However, such an explanation cannot be readily offered when survivals occur following the intraperitoneal introduction of feces containing many other bacteria besides *B. coli*. Are the colon bacilli present in the feces solely responsible for the production of peritonitis and death? Is the immunity produced general and is it specific or nonspecific, or is one dealing with a peritoneal, cellular, nonspecific, local immunity? The experiments presented in this communication are attempts to answer, at least partly, these questions. We are presenting in this paper only the cellular reactions observed in the peripheral circulation, the peritoneal exudate and the tissues. The rôle of the so-called humoral elements will be presented in another communication.

## EXPERIMENTAL PROCEDURES

Fecal material obtained from the lower part of the small bowel and the large bowel of dogs was mixed thoroughly with a 0.9 per cent sodium chloride solution and filtered through gauze. These prepared feces were injected into other dogs to produce acute fecal peritonitis. Four grams of feces in 20 cc. of saline solution was injected intraperitoneally into each animal.

A number of the dogs were immunized by intraperitoneal injections of living colon bacilli (our strain 300). The method of immunization was described in detail by Steinberg and Goldblatt.<sup>3</sup> Other dogs were immunized by subcutaneous

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\* Submitted for publication, Jan. 26, 1929.

\* From the Division of Laboratories and Research, Toledo Hospital.

\* This communication is a part of an experimental study on "Recovery in Peritonitis" made possible by a grant from the American Medical Association.

1. Steinberg, B., and Goldblatt, H.: Peritonitis: IV. Production of Active Immunity Against the Fatal Outcome of Experimental Fecal Peritonitis, Arch. Int. Med. **42**:415 (Sept.) 1928.

2. Goldblatt, H., and Steinberg, B.: Peritonitis: III. Active Immunization Against Experimental B. Coli Peritonitis, Arch. Int. Med. **41**:42 (Jan.) 1928.

3. Steinberg and Goldblatt (footnotes 1 and 2).

injections of living *B. coli*. A number of dogs were immunized by intraperitoneal injections of formaldehyde-killed *B. coli* (these, suspended in saline solution, were allowed to stand in 0.1 per cent formaldehyde for six hours). The same method of immunization was employed irrespective of the route or the state of the bacteria.

Prior to the production of the peritonitis, total and differential counts of the white cells of the peripheral blood were made. Following the onset of the peritonitis, total and differential counts of the white cells of the peripheral blood and of the peritoneal exudate were made at half hourly or hourly intervals. Supravital dyes (neutral red and janus green) were used in studying the peritoneal exudate, which was obtained by abdominal puncture with sterile glass capillary pipets. A neutral red stock solution was made up of 0.1 Gm. of the dye in 10 cc. of absolute alcohol; 0.5 cc. of the neutral red stock solution and 0.4 cc. of a saturated solution of janus green in absolute alcohol was added to 10 cc. of absolute alcohol. Dry smears were made from the dilute mixture of dyes. A drop of the peritoneal exudate was placed on the cover slip and inverted on the dry dye film. At short intervals, dogs were killed with chloroform and sections were taken from the omentum, parietal peritoneum, mesentery, diaphragm, intestine, mesenteric lymph node, liver, spleen and kidney, from approximately the same locations. The tissue was fixed in Zenker-formaldehyde without acetic acid and stained with hematoxylin-eosin and Gram stains. Thus, at short intervals following the onset of peritonitis, the peripheral blood, the peritoneal exudate and the tissue reactions were correlated.

*Fecal Peritonitis in Normal, Nonimmune Animals.*—In a previous communication, it was pointed out that when a sufficient amount of fecal material is injected into the peritoneal cavity of a dog, the animal develops a general peritonitis and succumbs within twenty-four hours. In these experiments, the duration of life of nonimmunized dogs with the peritoneum soiled with fecal material did not exceed eight hours. However, different samples and varying amounts of feces altered the survival period of the animals. In some of our experiments (unpublished), the intraperitoneal introduction of 2 Gm. of feces resulted in the survival of the animals for six days. We therefore used, for all the animals in these experiments, feces from the same stock, and administered it to them in equal amounts. Ten control dogs that had received injections of equal amounts of feces (4 Gm. in a 0.9 per cent sodium chloride solution) died in from seven to eight hours. It therefore became incumbent on us to study the cellular reactions within the first eight hours. Six dogs were used in the study of the cellular response to fecal peritonitis in normal nonimmune animals. One dog was allowed to die from the peritoneal infection; it died in seven and three-quarter hours after the onset of the infection. A second dog was killed at the end of one hour; a third at the end of two hours; a fourth at the end of three hours; a fifth at the end of four hours, and a sixth at the end of six hours after peritonitis was produced.

*Fecal Peritonitis in Immune Animals.*—The dogs were immunized by intraperitoneal injections of living colon bacilli (our strain 300, isolated from the blood of a patient dying with colon bacillus bacteremia). Thirteen dogs were used in this series. Twelve of these animals received intraperitoneally equal amounts of fecal material in saline solution (4 Gm. of feces in a 0.9 per cent sodium chloride solution); four of them were allowed to survive to confirm the efficacy of the immunization. The peritoneal exudate, the peripheral blood and the tissue reaction were studied in the other eight dogs. The animal that did not get any fecal material was killed and the tissues studied for reactions produced by the immunization. Of the eight dogs with fecal peritonitis, one was killed one hour after the

onset of peritonitis, another at the end of three hours, a third at the end of four hours, a fourth at the end of six hours, two at the end of eight hours, a seventh at the end of twelve hours, and the eighth at the end of twenty-four hours.

In the immunized dog without peritonitis, the total white cell count of the peripheral blood was 34,300. Polymorphonuclears constituted 91 per cent, mononuclears 4 per cent and lymphocytes 5 per cent. The peritoneal fluid showed only an occasional epithelial cell. The omentum and the parietal peritoneum contained cellular areas from 20 to 70 microns in width. The greater number of cells con-

TABLE 1.—*The Peripheral Blood and the Peritoneal Exudate in a Normal, Non-immune Dog with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis (Prior to onset of peritonitis)	Peripheral Blood		Peritoneal Exudate		
	Total White Count per C.Mm.	Differential Count	Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
	22,150	Polymorpho-nuclears.... 76% Lymphocytes 24%			
1	6,950	Polymorpho-nuclears.... 45% Lymphocytes 55%	1,300	Polymorpho-nuclears.... 81% Epithelial cells 14% Lymphocytes 5%	Polymorpho-nuclears.... 81% Mononuclears 19%
2	4,600	Polymorpho-nuclears.... 38% Lymphocytes 62%	6,200	Polymorpho-nuclears.... 86% Epithelial cells 9% Lymphocytes 5%	Polymorpho-nuclears.... 84% Mononuclears 16%
3	3,400	Polymorpho-nuclears.... 10% Lymphocytes 90%	27,750	Polymorpho-nuclears.... 90% Epithelial cells 8% Lymphocytes 2%	Polymorpho-nuclears.... 92% Mononuclears 8%
4	2,350	Polymorpho-nuclears.... 34% Lymphocytes 66%	26,950	Polymorpho-nuclears.... 91% Epithelial cells 7% Lymphocytes 2%	Polymorpho-nuclears.... 90% Mononuclears 10%
5	4,150	Polymorpho-nuclears.... 50% Lymphocytes 50%	26,300	Polymorpho-nuclears.... 95% Lymphocytes 5%	Polymorpho-nuclears.... 92% Mononuclears 8%
6	4,500	Polymorpho-nuclears.... 50% Lymphocytes 50%	14,900	Polymorpho-nuclears.... 89% Monocytes... 7% Lymphocytes 4%	Polymorpho-nuclears.... 88% Monocytes... 8% Mononuclears 4%
7	6,800	Polymorpho-nuclears.... 62% Lymphocytes 38%	14,100	Polymorpho-nuclears.... 80% Monocytes... 10% Lymphocytes 10%	Polymorpho-nuclears.... 86% Monocytes... 16% Mononuclears 10%
7½	7,400	Polymorpho-nuclears.... 68% Lymphocytes 32%	14,400	Polymorpho-nuclears.... 86% Monocytes... 6% Lymphocytes 8%	Polymorpho-nuclears.... 84% Monocytes... 8% Mononuclears 8%
Outcome: Died 7¾ hours after onset of peritonitis.					

sisted of large mononuclears, the remaining cells were plump and fusiform with fairly vesicular nuclei. These cells had the appearance of young fibroblasts; however, in the same sections, we observed similar cells sprouting from the endothelium of capillaries, and we are designating them here as endothelial cells. The capillaries were slightly dilated, and contained a small number of red cells and a few polymorphonuclears. In places, there was formation of new capillaries, the total picture being that of granulation tissue.

*Immunization with Formaldehyde-Killed Bacteria and Production of Fecal Peritonitis.*—An attempt to produce immunity against fecal peritonitis by the intraperitoneal injection of heat-killed *B. coli* did not prove successful.<sup>1</sup> Heat destroyed the greater part of the antigenic properties of the colon bacillus. As



a part of another experiment (in collaboration with Dr. H. Goldblatt), formaldehyde-killed *B. coli* (strain 300) were injected into six dogs intraperitoneally and into five dogs subcutaneously. The immunizing procedures were otherwise similar to those employed with living bacteria. Each of the eleven dogs received intra-

TABLE 2.—*The Peripheral Blood and the Peritoneal Exudate in an Immune Dog with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis (Prior to onset of peritonitis)	Peripheral Blood		Peritoneal Exudate		
	Total White Count per C.Mm.	Differential Count	Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
	40,200	Polymorpho-nuclears.... 95% Lymphocytes 5%			
1	27,000	Polymorpho-nuclears.... 92% Lymphocytes 8%	50,500	Polymorpho-nuclears.... 99% Epithelial cells 1%	Polymorpho-nuclears.... 99% Mononuclears 1%
2	12,500	Polymorpho-nuclears.... 90% Lymphocytes 10%	98,600	Polymorpho-nuclears.... 99% Epithelial cells 1%	Polymorpho-nuclears.... 99% Mononuclears 1%
3	4,300	Polymorpho-nuclears.... 83% Lymphocytes 17%	186,500	Polymorpho-nuclears.... 100%	Polymorpho-nuclears.... 98% Mononuclears 2%
4	8,750	Polymorpho-nuclears.... 79% Lymphocytes 21%	197,000	Polymorpho-nuclears.... 98% Mononuclears 2%	Polymorpho-nuclears.... 96% Monocytes... 4%
5	13,000	Polymorpho-nuclears.... 86% Lymphocytes 14%	216,000	Polymorpho-nuclears.... 93% Mononuclears 5%	Polymorpho-nuclears.... 93% Monocytes... 7%
6	23,700	Polymorpho-nuclears.... 84% Lymphocytes 16%	238,000	Polymorpho-nuclears.... 90% Mononuclears 10%	Polymorpho-nuclears.... 91% Monocytes... 7% Clasmatocytes 2%
7	26,400	Polymorpho-nuclears.... 82% Lymphocytes 18%	252,000	Polymorpho-nuclears.... 90% Lymphocytes 2% Mononuclears 8%	Polymorpho-nuclears.... 85% Monocytes... 8% Clasmatocytes 7%
8	43,500	Polymorpho-nuclears.... 81% Lymphocytes 19%	281,150	Polymorpho-nuclears.... 90% Mononuclears 10%	Polymorpho-nuclears.... 88% Monocytes... 10% Clasmatocytes 2%
9	48,500	Polymorpho-nuclears.... 82% Lymphocytes 18%	228,000	Polymorpho-nuclears.... 90% Mononuclears 10%	Polymorpho-nuclears.... 87% Monocytes... 8% Clasmatocytes 5%
10	50,000	Polymorpho-nuclears.... 87% Lymphocytes 13%	217,000	Polymorpho-nuclears.... 87% Mononuclears 13%	Polymorpho-nuclears.... 82% Monocytes... 10% Clasmatocytes 8%
11	52,000	Polymorpho-nuclears.... 92% Lymphocytes 8%	209,000	Polymorpho-nuclears.... 85% Mononuclears 15%	Polymorpho-nuclears.... 80% Monocytes... 8% Clasmatocytes 12%
12	57,000	Polymorpho-nuclears.... 92% Lymphocytes 8%	212,000	Polymorpho-nuclears.... 85% Mononuclears 15%	Polymorpho-nuclears.... 80% Monocytes... 11% Clasmatocytes 9%

Outcome: Killed at end of 12 hours after onset of peritonitis.

peritoneally 4 Gm. of feces in 20 cc. of a 0.9 per cent sodium chloride solution. All died in from seven to eighteen hours. Apparently, formaldehyde had destroyed all the antigenic properties of *B. coli*. The peripheral blood, the peritoneal exudate and the tissue of one of the dogs that received intraperitoneal injections of formaldehyde-killed bacteria were studied. The dog died in seven hours fifty minutes after the onset of peritonitis.

The peritoneal exudate, hour by hour, was similar to that observed in normal, nonimmune dogs with fecal peritonitis. Monocytes and clasmatoocytes, however, appeared at the end of the fifth hour. At death, the clasmatoocytes numbered 6 per cent and the monocytes 9 per cent. The omentum, the peritoneum and the mesentery showed mononuclears and endothelial cells, as observed in the sixth and eighth hour of fecal peritonitis in the immune dogs. The autopsy showed hemorrhagic peritonitis with little fibrin and 560 cc. of a cloudy, red, free fluid.

*Subcutaneous Immunization with Living Colon Bacilli and Production of Fecal Peritonitis.*—Three dogs were immunized subcutaneously with living colon bacilli. The immunizing method was the same as that employed in the intraperitoneal immunization. Each of the three animals received an intraperitoneal injection of 4 Gm. of

TABLE 3.—*The Peripheral Blood and the Peritoneal Exudate in a Dog (Immunized with Formaldehyde-Killed Bacteria) with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis	Peripheral Blood: Total White Count per C.Mm.	Peritoneal Exudate			
		Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation	
(Prior to onset of peritonitis)	19,850				
1	8,100	1,800	Polymorphonuclears 92% Lymphocytes..... 6% Epithelial cells..... 2%	Polymorphonuclears 98% Mononuclears..... 2%	
2	5,200	3,940	Polymorphonuclears 96% Epithelial cells..... 4%	Polymorphonuclears 99% Mononuclears..... 1%	
3	3,300	7,200	Polymorphonuclears 91% Lymphocytes..... 4% Epithelial cells..... 5%	Polymorphonuclears 93% Mononuclears..... 7%	
4	2,700	11,000	Polymorphonuclears 94% Lymphocytes..... 2% Epithelial cells..... 4%	Polymorphonuclears 95% Mononuclears..... 5%	
5	3,850	31,600	Polymorphonuclears 97% Mononuclears..... 3%	Polymorphonuclears 95% Monocytes..... 4% Clasmatoocytes..... 1%	
6	(Not taken)	(Not taken)	(Not taken)	(Not taken)	
7	4,450	80,000	Polymorphonuclears 91% Mononuclears..... 9%	Polymorphonuclears 88% Monocytes..... 8% Clasmatoocytes..... 4%	
7½	6,200	64,000	Polymorphonuclears 84% Mononuclears..... 16%	Polymorphonuclears 85% Monocytes..... 9% Clasmatoocytes..... 6%	
Outcome: Died 7½ hours after onset of peritonitis.					

feces in 20 cc. of a 0.9 per cent sodium chloride solution. Two of the animals were allowed to survive. The peritoneal exudate and the peripheral blood of the third were studied for twelve hours; then the dog was killed and the cellular reactions of the tissue were studied. The peritoneal exudate, during the twelve hours, showed a polymorphonuclear percentage that varied from 93 to 100. Monocytes appeared at the end of the third hour and never exceeded 6 per cent. The bacterial content of the peritoneal smears and the polymorphonuclear phagocytosis were similar to what had been seen in the case of the intraperitoneally immunized dogs. The omentum, the peritoneum and the mesentery at the end of twelve hours showed 91 per cent polymorphonuclears, 3 per cent mononuclears and 6 per cent endothelial cells. A number of polymorphonuclears in the tissue contained phagocytosed bacteria. The autopsy showed 721 cc. of a dirty gray fluid with some flakes of fibrin, a small amount of fibrin on some loops of bowel and a slight injection of the peritoneum, the mesentery and the diaphragm.

SUMMARY OF EXPERIMENTAL OBSERVATIONS

The white cells of the peripheral blood both in the immune and in the nonimmune animals appreciably decreased in number at the end of the first hour; this decrease continued and reached its lowest point at the end of four hours. From that hour the peripheral white cells began to increase in number. In nonimmune dogs, death occurred, as

TABLE 4.—*The Peripheral Blood and the Peritoneal Exudate in a Subcutaneously Immunized Dog with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis	Peripheral Blood		Peritoneal Exudate		
	Total White Count per C.Mm.	Differential Count	Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
(Prior to onset of peritonitis)	28,200	Polymorpho-nuclears.... 82% Lymphocytes 18%			
1	27,750	Polymorpho-nuclears.... 78% Lymphocytes 22%	9,500	Polymorpho-nuclears.... 100%	Polymorpho-nuclears.... 100%
2	18,600	Polymorpho-nuclears.... 81% Lymphocytes 19%	28,650	Polymorpho-nuclears.... 98% Lymphocytes 2%	Polymorpho-nuclears.... 100%
3	27,600	Polymorpho-nuclears.... 81% Lymphocytes 19%	67,600	Polymorpho-nuclears.... 98% Mononuclears 2%	Polymorpho-nuclears.... 99% Monocytes... 1%
4	32,100	Polymorpho-nuclears.... 80% Lymphocytes 20%	107,250	Polymorpho-nuclears.... 99% Mononuclears 1%	Polymorpho-nuclears.... 99% Monocytes... 1%
5	47,000	Polymorpho-nuclears.... 85% Lymphocytes 15%	180,000	Polymorpho-nuclears.... 96% Mononuclears 4%	Polymorpho-nuclears.... 98% Monocytes... 2%
6	45,000	Polymorpho-nuclears.... 89% Lymphocytes 11%	160,500	Polymorpho-nuclears.... 93% Mononuclears 7%	Polymorpho-nuclears.... 98% Monocytes... 2%
7	(Not taken)	(Not taken)	(Not taken)	(Not taken)	(Not taken)
8	42,500	Polymorpho-nuclears.... 91% Lymphocytes 9%	161,100	Polymorpho-nuclears.... 93% Mononuclears 7%	Polymorpho-nuclears.... 94% Monocytes... 6%
9	51,050	Polymorpho-nuclears.... 89% Lymphocytes 11%	160,500	Polymorpho-nuclears.... 95% Mononuclears 5%	Polymorpho-nuclears.... 95% Monocytes... 2%
10	70,500	Polymorpho-nuclears.... 86% Lymphocytes 14%	149,000	Polymorpho-nuclears.... 95% Mononuclears 5%	Polymorpho-nuclears.... 98% Monocytes... 2%
11	(Not taken)	(Not taken)	(Not taken)	(Not taken)	(Not taken)
12	79,200	Polymorpho-nuclears.... 88% Lymphocytes 12%	127,000	Polymorpho-nuclears.... 97% Mononuclears 3%	Polymorpho-nuclears.... 98% Monocytes... 2%

Outcome: Killed at end of 12 hours after onset of peritonitis.

a rule, before the white cells reached their normal level as determined before the infection. In immune dogs, the white cells increased in number from the fourth hour and in eight hours exceeded the pre-infection count. The immune animals evidenced a more ready mobilization of leukocytes following an initial leukopenia. The number of polymorphonuclears in the peripheral blood decreased relatively and absolutely with the decrease of the total number of the white cells, while the number of lymphocytes relatively increased. With the rise

of the total number of white cells, the previous polymorphonuclear-lymphocyte ratio was established.

Coincident with the fall of the peripheral leukocyte count, cells made their appearance in the peritoneal exudate. In fifteen minutes after the onset of the infection, cells were found in the exudate. In immune animals, cells appeared in greater number and more rapidly than in nonimmune dogs. At the end of the second hour, the cell count of an immune dog exceeded by from three to four times the largest number of cells of a nonimmune dog during any hour. The polymorphonuclears constituted, for the first three hours, from 98 to 100 per cent of the



Fig. 1.—Smear of the peritoneal exudate of fecal peritonitis one hour after onset in a normal, nonimmune dog. A large number of bacteria of various kinds may be seen, including three polymorphonuclear leukocytes. These do not show any phagocytosis.

cells in both the immune and nonimmune dogs. From the fourth hour, monocytes appeared in the immune animal. At the end of the sixth hour, clasmatoocytes began to appear. At the end of eight hours, both monocytes and clasmatoocytes constituted approximately 12 per cent of the total number of cells, the other cells being polymorphonuclears. In nonimmune animals, monocytes appeared at the end of the sixth hour and constituted from 8 to 10 per cent of the total number of cells.

The polymorphonuclears showed marked phagocytic activities in non-immune animals. Practically all the polymorphonuclears were loaded with

bacteria, but there were apparently too many bacteria for the number of cells; there were large numbers of free bacteria throughout the course of the infection. In immune animals, practically all the bacteria were phagocytosed at the end of two hours and, owing to the large number of cells, only some of them contained bacteria. As far as the peritoneal exudate was concerned, the struggle with the bacteria was over in two or three hours. The tissue of the nonimmune dogs showed a paucity of leukocytes. At the end of seven and three-quarter hours, the tissue of the nonimmune animal with the largest number of polymorphonuclears at its disposal actually had far less polymorphonuclears than an immune animal at the end of an hour after the onset of peritonitis. The polymorphonuclears of the tissue were likewise phagocytic. In the

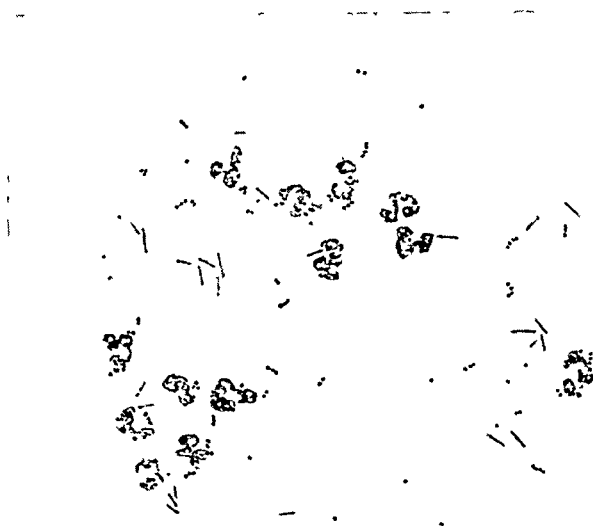


Fig. 2.—Smear of the peritoneal exudate of fecal peritonitis seven and three-quarter hours after onset in a normal, nonimmune dog. A large number of bacteria of various kinds may be seen, including twelve polymorphonuclears, most of them containing phagocytosed bacteria.

fourth hour, the tissue of the immune animal showed a number of mononuclear cells with ingested red and white cells.

Intraperitoneal injections of formaldehyde-killed bacteria, which do not immunize, evoked in a fecal peritonitis a peritoneal exudate which at the end of seven and five-sixth hours showed a small number of white cells, with the monocytes and clasmatocytes constituting 15 per cent.

Subcutaneous immunization, which resulted in an actual immunity, produced a rapid mobilization of cells in the peripheral blood and a large number of cells in the peritoneal exudate, which contained only 2 per cent monocytes, and 98 per cent polymorphonuclears.

## COMMENT

The purpose of this work was essentially to determine the character of the cellular activity in fecal peritonitis following active immunization with colon bacilli. However, the results of the experiments placed us in the midst of a controversy as to the type of cell responsible for the immunity and as to whether the immunity produced is local. This controversy began, in part, with Metchnikoff,<sup>4</sup> who asserted that the polymorphonuclears (microphages) are the phagocytic cells and that the mononuclears (macrophages) are not concerned with phagocytosis of bacteria but rather with the disposal of disabled microphages. Since

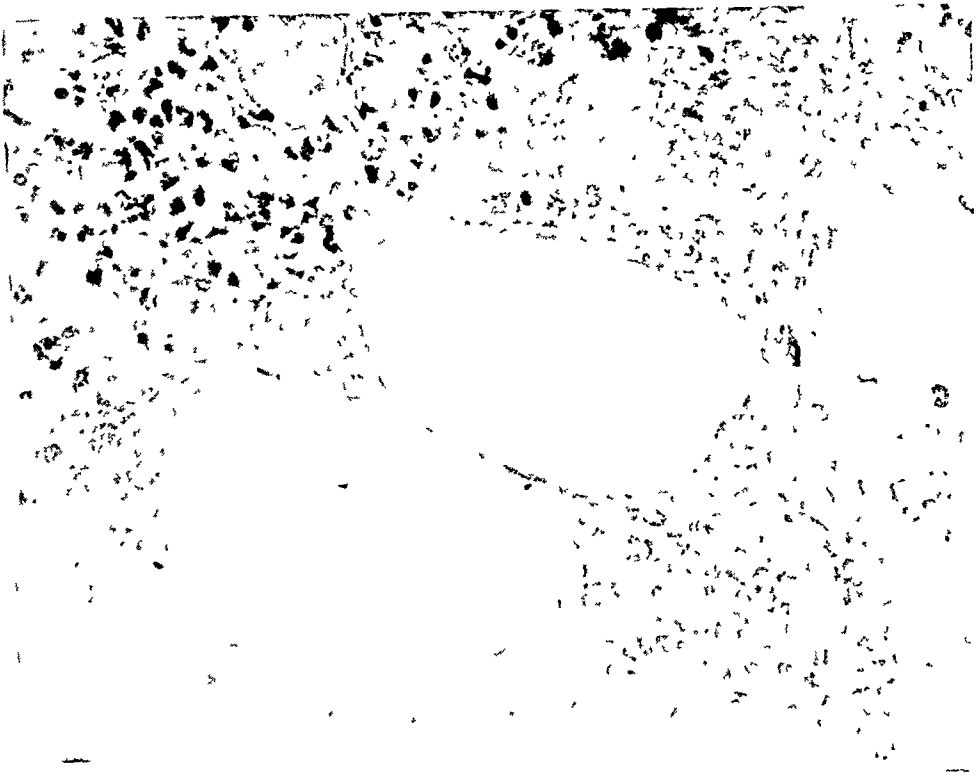


Fig. 3—Section of omentum at the end of seven and three-quarter hours of fecal peritonitis in a normal, nonimmune dog. A moderate number of polymorphonuclears and mononuclears may be seen

then, other investigators have observed that the mononuclears phagocytose not only polymorphonuclears but also bacteria; these mononuclears have been variously termed clasmatoocytes by Ranvier, adventitial cells by Marchand, pyrrhol cells by Goldman, endothelial leukocytes by Mallory, polyblasts by Maximow and round rhagiocrins by Renault. Durham,<sup>5</sup> Bordet,<sup>6</sup> Wallgren,<sup>7</sup> Buxton and Torrey,<sup>8</sup> Zange-

4. Metchnikoff, E.: *Virchows Arch f path Anat* **107**:209, 1887

5. Durham, A. E.: *J Path & Bact* **4**:338, 1897.

6. Bordet, J.: *Ann de l'inst. Pasteur* **11**:177, 1897

7. Wallgren, A.: *Beitr. z path Anat u z allg Path* **25**:206, 1899.

8. Buxton, B. H., and Torrey, J. C.: *J M Research* **15**:3, 1906

meister and Gans<sup>9</sup> and Kanai<sup>10</sup> were some of the investigators who observed phagocytosis of bacteria by mononuclears and ascribed to these mononuclears the chief rôle in the disposal of the bacteria. Besredka<sup>11</sup> introduced the conception of local immunity and Gay<sup>12</sup> and his collaborators associated these mononuclears, or clasmatoocytes, with local immunity. Gay and his co-workers asserted that the formation of antibodies is coincident with the appearance of clasmatoocytes and that local protection is dependent on a local increase in the number of clasmatoocytes.

Other investigators, among them von Büngner,<sup>13</sup> Helly,<sup>14</sup> Cunningham<sup>15</sup> and Freedlander and Toomey,<sup>16</sup> observed that there was a preponderance of polymorphonuclears within the first twenty-four hours after the introduction of bacteria or particulate matter. Metalnikov



Fig. 4.—Smear of the peritoneal exudate of fecal peritonitis one hour after onset in an intraperitoneally immunized dog. There are six polymorphonuclears containing many phagocytosed bacteria. There are only three free bacteria.

9. Zangemeister, W., and Gans, H.: *München. med. Wchnschr.* **56**:793, 1909.

10. Kanai, S.: *Verhandl. d. jap. path. Gesellsch.* **1**:126, 1919.

11. Besredka, A.: *Ann. de l'inst. Pasteur* **35**:421, 1921; *Local Immunization: Specific Dressings*, trans. by Plotz, Baltimore, Williams & Wilkins, 1927.

12. Gay, F. P., and Morrison, L. F.: *J. Infect. Dis.* **33**:338, 1923. Gay, F. P.: *Physiol. Rev.* **4**:191, 1924. Gay, F. P., and Linton, R. W.: *Proc. Soc. Exper. Biol. & Med.* **23**:325, 1926. Gay, F. P.; Clark, A. R., and Linton, R. W.: *A Histologic Basis for Local Resistance and Immunity to Streptococcus: VII. Studies in Streptococcus Infection and Immunity*, *Arch. Path.* **1**:857 (June) 1926.

13. Von Büngner: *Beitr. z. path. Anat. u. z. allg. Path.* **19**:33, 1896.

14. Helly, K.: *Beitr. z. path. Anat. u. z. allg. Path.* **37**:171, 1905.

15. Cunningham, R. S.: *Am. J. Physiol.* **59**:1, 1922.

16. Freedlander, S. O., and Toomey, J. A.: *J. Exper. Med.* **47**:663, 1928.

and Toumanoff,<sup>17</sup> in a recent article, again demonstrated the early appearance of polymorphonuclears in the peritoneal cavity and observed a more rapid phagocytosis in vaccinated animals and the late appearance of clasmatocytes.

In our experiments, the criterion of a successful immunization was survival of the animal. Lack of immunity resulted in death. Our work suggests that the issue of death or survival under the conditions of the experiments is decided within the first eight hours after the onset of the infection. This assumption is based on the death of the

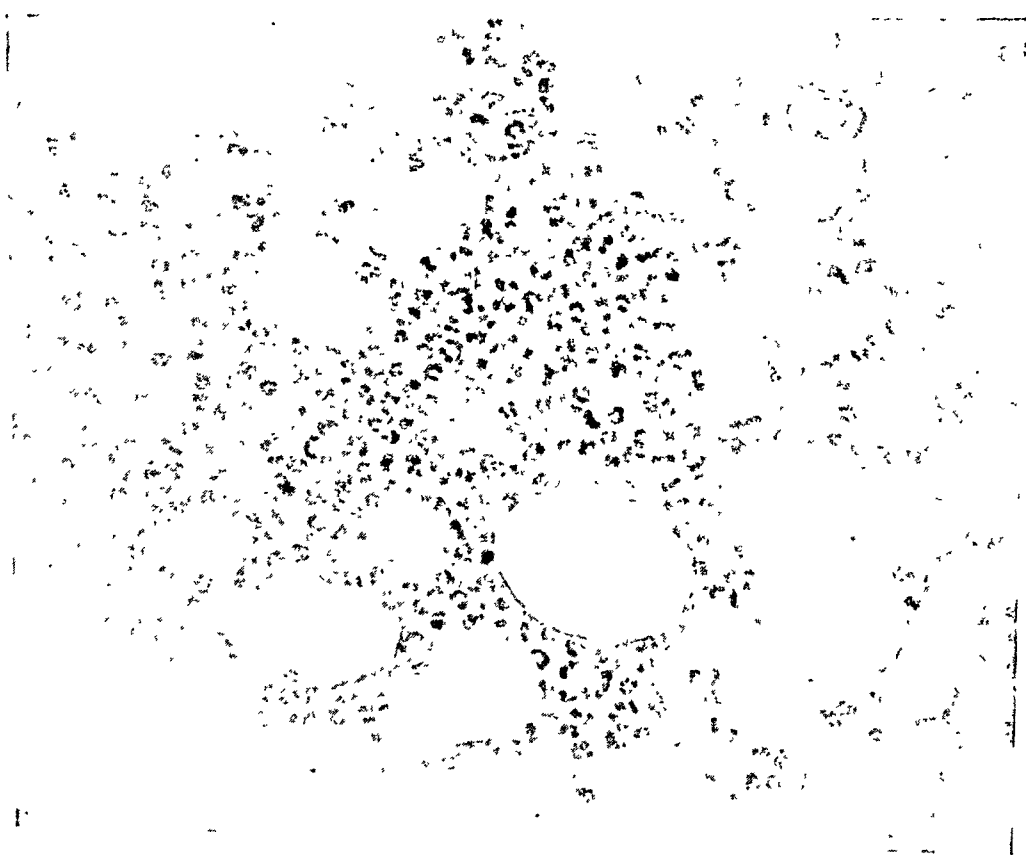


Fig. 5.—Section of omentum at the end of one hour of fecal peritonitis in an intraperitoneally immunized dog. There is a fairly large number of polymorphonuclears free in the tissue.

control nonimmune animals within eight hours, and the practically total disposal of the free bacteria in the immune animals within those hours. If this assumption is true, the polymorphonuclear is apparently the cell essentially concerned with the primary disposal of the bacteria in the immunized animals with fecal peritonitis.

It is not within the scope of this paper to follow the fate of the polymorphonuclears after the phagocytosis of bacteria. The observa-

17. Metalnikov, S., and Toumanoff, K.: *Ann. de l'inst. Pasteur* **38**:22, 1925.



tions of investigators from Metchnikoff to Freedlander and Toomey agree as to the capacity of the clasmatoocyte to phagocytose polymorphonuclears. Metchnikoff's contention that the function of clasmatoocytes is to remove damaged microphages is further amplified by the assumption of Freedlander and Toomey that the ingestion of polymorphonuclears with bacteria by clasmatoocytes prevents a recurrence of bacterial activity. That such a recurrence of bacterial activity on the death of the cell is possible is suggested by the original demonstration by Metchnikoff (quoted by Besredka<sup>18</sup>) of viable phagocytosed bacteria within polymorphonuclears from ten to twelve days after phagocytosis.

Since most of the immunization was done intraperitoneally, it should have been possible to establish a local immunity. Local immunity as defined by Gay<sup>19</sup> "is an acquired, increased protection of some part of tissue superior to that existent elsewhere in the body. It is further a locally superior mechanism for the disposal of the particular micro-organism rather than a local mobilization of antibodies generally present in the body." Under the conditions of our experiments, we failed to observe any particular increased local cellular protection. The cellular response in the peritoneal cavity following colon bacillus immunization and fecal peritonitis was apparently a local mobilization of a general increase in cellular activity. The local peritoneal picture of granulation tissue in the immunized dog (Gay and his co-workers called attention to the thickening of the pleura in immunized animals) without peritonitis we assumed to be a healing inflammatory reaction in response to the introduction of an irritant—in this instance, colon bacillus. Furthermore, our subcutaneously immunized animal was as readily protected and showed a local reaction as rapid and extensive as did the intraperitoneally immunized dogs. Attempted intraperitoneal immunization with formaldehyde-killed colon bacilli resulted in peritoneal granulation tissue (observed in the dog with twelve hour peritonitis) but not in immunity. It is not unlikely that this granulation tissue is more prepared to combat infection than normal tissue; it is more vascular and hence commandeers more cells; and it contains the later cells of the healing process. However, in our experiments, this granulation tissue alone was not sufficient to establish immunity. Other factors, which were responsible for the ready mobilization of polymorphonuclears, were necessary.

#### SUMMARY

Active immunization with living colon bacilli, followed by fecal peritonitis, resulted in the first twenty-four hours in a cellular reaction

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18. Besredka (footnote 11, second reference).

19. Gay (footnote 12, first reference).

which was predominantly polymorphonuclear. The bacteria in the peritoneal cavity were phagocytosed largely by polymorphonuclears, and the phagocytosis was practically complete at the end of the first eight hours after the onset of peritonitis. The polymorphonuclears, evoked by colon bacillus immunization, acted as phagocytes of other bacteria in the peritoneal exudate than *B. coli*. The difference in the cellular reaction in the peritoneal exudate, the peripheral blood and the tissue between a nonimmune and an immune animal, under the conditions of these experiments, was quantitative. The immune animal mobilized polymorphonuclears more rapidly and mobilized a far greater number of them than the nonimmune animal. The factor in the colon bacillus that evoked this cellular activity was destroyed entirely by formaldehyde. The presence of white cells in the peritoneal exudate of immune animals with peritonitis, apparently represented a local manifestation of a general mobilization of these cells. The polymorphonuclears in the general circulation were apparently the first cells to appear at the point of bacterial invasion, and therefore they probably represented the first line of cellular defense against the bacterial infection.

# THE PATHOLOGIC ANATOMY IN TWENTY-EIGHT CASES OF ADDISON'S DISEASE \*

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In the original description of the disease which bears his name, Thomas Addison defined it as "a remarkable progressive feebleness of the patient without any apparent known cause, or as it is styled, asthenia, a discoloration of the skin and a disease of the suprarenal capsules."<sup>1</sup> Wilks,<sup>2</sup> who studied the pathologic anatomy in Addison's first cases, in 1862 and 1865 reported a total of thirty-three cases which coincided with the entity which Addison described. He included five of Addison's original cases, but discredited the others as not conforming to the entity and not intended to be included by Addison himself. Wilks described the suprarenal glands in the series as scrofulous and totally destroyed. Because the necrosis in the suprarenal glands did not resemble the necrosis ascribed to tuberculosis at that time, he was rather of the opinion that the glands presented a unique disease not identical with other tuberculous processes. In many of his cases were small tuberculous lesions of other parts of the body, both healed and active, but in none were these extensive. Wilks' excellent description of the gross aspect of the suprarenal glands, however, leaves little doubt that the lesions were the same as lesions that have been seen many times since and identified as tuberculosis by histologic study. Wilks mentioned enlarged lymph nodes and hyperplasia of the intestinal lymphoid tissue in several cases. He noted that the hearts were rather small, and in a few of the cases described another curious and still unexplained phenomenon, hyperplasia of Brunner's glands. In 1885, Coupland<sup>3</sup> reported a case of clinical Addison's disease in which both suprarenal glands were found to be markedly atrophic. He was able to find five

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\* Submitted for publication, April 22, 1929.

\* From the Division of Medicine, the Mayo Clinic.

\* Work done in the Section on Pathologic Anatomy.

1. Wilks, Samuel, and Daldy: On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules, in: A Collection of the Published Writings of Thomas Addison, London, The New Sydenham Society, 1868, p. 211.

2. Wilks, Samuel: On Disease of the Supra-Renal Capsules; or, Morbus Addisonii, Guy's Hosp. Rep. 8:1, 1862; Additional Cases of Supra-Renal Disease with Remarks, *ibid.* 11:23, 1865.

3. Coupland, Sidney: Atrophy of Adrenals with Addison's Disease, Tr. Path. Soc. Lond. 36:423, 1885.

similar cases in the literature. In 1892, Lewin<sup>4</sup> made an extremely comprehensive review of the literature up to that time.

Unfortunately, Addison's original description was used somewhat loosely and numerous cases were reported merely because the patients had brownish pigmentation of the skin with or without suprarenal lesions. Also many suprarenal lesions of different types, unilateral and bilateral, small and extensive, were reported as being caused by Addison's disease without the typical clinical syndrome. Lewin's two series included 871 cases. These are difficult to tabulate because they were described by so many different authors in so many different ways. Lewin cited 639 of these as typical cases; the suprarenal glands were normal in 72 of them and in 233 there was no pigmentation. Among the diseased conditions of the suprarenal glands, tuberculosis or probable tuberculosis was found in 254. Bacilli of tuberculosis were said to have been found in the suprarenal glands in seven cases. A few cases were described as being cases of atrophy or degeneration, carcinoma, cysts, amyloidosis, gumma, echinococcus cysts and complete aplasia. The pathologic anatomy of the suprarenal glands in the other cases was not definitely reported. There was associated pulmonary tuberculosis in 256 cases, and renal tuberculosis in 16. In 1907, Hedinger<sup>5</sup> reported a series of fifteen cases of Addison's disease, in fourteen of which there was tuberculosis and in one case atrophy of the suprarenal glands. He stressed the fact that a status thymicolymphaticus was found in seven cases, including the case of atrophy, and that in five more there was generalized hyperplasia of the lymph nodes.

The largest recent series was reported by Coneybeare and Millis,<sup>6</sup> and comprised twenty-nine cases with necropsies, observed in Guy's Hospital between 1904 and 1923. Of these, there was bilateral fibrocaseous tuberculosis of the suprarenal glands in twenty-two and simple atrophy in six. In one case, suprarenal tissue was not found. In the twenty-two cases of tuberculosis of the suprarenal glands, there was active tuberculosis elsewhere in the body in six, and in all there were tuberculous scars in the lungs. The question of gumma of the suprarenal glands as a cause of Addison's disease was discussed by Schaffner and Howard<sup>7</sup> in 1916. They cited two cases described by Taylor and one by Jacquet and Segary in which *Treponema pallidum* was demonstrated. Amyloidosis of the suprarenal glands has been described

4. Lewin, G.: Ueber Morbus addisonii, Charité-Ann. **17**:536, 1892.

5. Hedinger, Ernst: Ueber die Kombination von Morbus addisonii mit Status lymphaticus, Frankfurt. Ztschr. f. Path. **1**:527, 1907.

6. Coneybeare, J. J., and Millis, G. C.: Observations on Twenty-Nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904 and 1923, Guy's Hosp. Rep. **74**:369, 1924.

7. Schaffner, P. M., and Howard, Tasker: Addison's Disease of Syphilitic Origin: Report of a Case, New York M. J. **103**:1026, 1916.

several times since Lewin's article appeared. Most of the clinical descriptions of these cases are not convincing, but the cases of Bittorf,<sup>8</sup> Schlesinger,<sup>9</sup> McCutcheon,<sup>10</sup> Hunter and Rush<sup>11</sup> and Philpott<sup>12</sup> seem fairly typical. In 1926, Loeper and Ollivier<sup>13</sup> described a case of bilateral fatty transformation of the suprarenal glands with typical addisonian symptoms. As has been mentioned, various cases of carcinoma have been reported. Greenhow<sup>14</sup> reported two cases and Bristow one case of complete destruction of the suprarenal glands by carcinoma. Pigmentation was not present in any of these cases. Wilks was rather emphatic in stating that carcinoma of the suprarenal glands was not a cause of Addison's disease. The cases of atrophy are interesting. Recently, Brenner<sup>15</sup> reported five cases and commented on the subject in considerable detail. He rejected the theory that the condition is congenital hypoplasia of the glands associated with a status thymicolymphaticus and does not believe that it is identical with healed atypical tuberculosis or with any other condition that can be identified. Chronic inflammation of indefinite etiology is questionable as a cause of atrophy. Brenner inclined more toward the opinion that the condition is one of simple atrophy, possibly due to slow necrosis from some toxin with special affinity for the suprarenal glands. The remaining cells undergo compensatory hypertrophy and multiply to form adenoma-like nodules. These cells are again attacked or undergo atrophy of exhaustion. The cortex is primarily involved and later the medulla. In Kiefer's<sup>16</sup> case, adenoma-like regeneration was striking. Recently, Philpott reported 14 cases of Addison's disease found in the course of 2,550 consecutive necropsies. The suprarenal lesions were as follows: tuberculosis, seven; metastatic carcinoma, four; mycosis fungoides, one; simple atrophy, one, and amyloidosis, one.

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8. Bittorf, A.: Beiträge zur Pathologie der Nebennieren, *Deutsches Arch. f. klin. Med.* **100**:116, 1910.

9. Schlesinger, Hermann: Subakute Insuffizienz der Nebennieren bei Amyloidose, nebst Bemerkungen über den Morbus addisonii, *Wien. klin. Wchnschr.* **30**:99, 1917.

10. McCutcheon, Morton: The Relation of Addison's Disease to Amyloidosis, *Am. J. M. Sc.* **166**:197, 1923.

11. Hunter, W. C., and Rush, H. P.: Amyloidosis of the Adrenals as a Cause of Addison's Disease, *Ann. Clin. Med.* **5**:404, 1926.

12. Philpott, N. W.: Addison's Disease in Association with Amyloidosis, *Ann. Int. Med.* **1**:613, 1927-1928.

13. Loeper, M., and Ollivier, J.: Métamorphose adipeuse des deux capsules surrenales avec metanodermie, *Bull. et mém. Soc. méd. d. hôp. de Paris* **2**:312, 1926.

14. Greenhow, E. H.: Cancer of the Supra-Renal Capsules, *Tr. Path. Soc. Lond.* **24**:238, 1872-1873.

15. Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Suprarenals, *Quart. J. M.* **22**:121, 1928.

16. Kiefer, Hans: Addisonsche Erkrankung infolge chronischer Nebennierendystrophie mit adenomartigen Regeneraten, *Arch. f. path. Anat.* **265**:472, 1927.

TABLE 1.—Summary of Pathologic Anatomy of Suprarenal Glands

Case	Year	Ne- cropsy, and Sex	Suprarenal Glands		Acid-Fast Bacilli in Tissue	Suprarenal Tissue Remaining
			Gross	Histologic		
1	1910	35 M	Both enlarged, typical fibrosis with necrotic areas	Advanced tuberculosis, proliferative type	—	A few small islands of cortex; a few hypertrophic adenomas
2	1914	47 M	Left large with typical necrosis; right small fibrous mass	Advanced tuberculosis, proliferative and necrotic type	—	Several small islands of cortex
3	1915	43 M	Both enlarged, typical necrosis	Advanced tuberculosis, necrotic type, very inactive	—	A few small islands of cortex; a few hypertrophic adenomas
4	1917	39 M	Both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few hypertrophic adenomas
5	1917	40 F	Right enlarged, typical necrosis; left encapsulated abscess	Advanced tuberculosis, necrotic type	—	Several small islands of cortex; several hypertrophic adenomas
6	1920	40 F	Both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	..	None*
7	1921	41 M	Right large, typical necrosis; left small, typical necrosis	Advanced tuberculosis, proliferative type	..	Several small islands of cortex; many hypertrophic adenomas
8	1922	32 M	Both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few hypertrophic adenomas
9	1923	31 M	Both very small and dark brown	Marked atrophy with some non-specific chronic inflammatory reaction	..	Approximately 5 per cent of cortex and 20 per cent of medulla
10	1923	55 M	Both enlarged, 21 and 15 Gm.; typical necrosis	Advanced tuberculosis, necrotic type	..	A few small islands of cortex; a few hypertrophic adenomas
11	1924	25 M	Both enlarged, 16 and 16 Gm.; typical necrosis	Advanced tuberculosis, necrotic type	..	A few small islands of cortex; a few hypertrophic adenomas
12	1925	69 M	Both slightly enlarged, typical necrosis	Moderately advanced tuberculosis, necrotic type	+ (many)	Approximately 10 per cent of cortex
13	1925	33 M	Left complete calcification; right two very small nodules	Right, advanced atrophy	..	Approximately 5 per cent of right suprarenal gland
14	1925	50 M	Both typical necrosis	Advanced tuberculosis, proliferative type	+ (few)	Several small areas of cortex; many hypertrophic adenomas
15	1925	34 M	Very large, 27 and 23 Gm.; both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few small islands of cortex; a few hypertrophic adenomas
16	1925	35 F	Normal size, both typical necrosis	Advanced tuberculosis, necrotic type	+ (few)	Several hypertrophic adenomas
17	1925	40 F	Both normal size; necrosis with marked calcification	Advanced tuberculosis, necrotic type with marked calcification	..	A few small islands of cortex
18	1925	65 M	Both small, typical necrosis	Advanced tuberculosis, necrotic type	—	A few small islands of cortex; a few hypertrophic adenomas
19	1925	26 M	Both typical necrosis with abscesses	Advanced tuberculosis, proliferative type with abscesses	+ (few)	Many hypertrophic adenomas
20	1927	45 F	Both typical necrosis	Advanced tuberculosis, necrotic type	+ (many)	A few small islands of cortex; a few hypertrophic adenomas

\* Material for complete study not available.

TABLE 1.—*Summary of Pathologic Anatomy of Suprarenal Glands—Continued*

Case	Ne-cropsy, and Year	Age Sex	Suprarenal Glands		Acid-Fast Bacilli in Tissue	Suprarenal Tissue Remaining
			Gross	Histologic		
21	1927	48 M	Both typical necrosis, enlarged, 23 and 21 Gm.	Advanced tuberculosis, proliferative and necrotic type	+	Several small islands of cortex
22	1927	45 M	Both typical necrosis	Advanced tuberculosis, necrotic type	+	A few small islands of cortex; many hypertrophic adenomas; one small island of medulla
23	1927	58 M	Right small, left large, both typical necrosis	Advanced tuberculosis, necrotic type	+	A few small islands of cortex; a few hypertrophic adenomas
24	1927	48 M	Normal size; both typical necrosis	Advanced tuberculosis, proliferative type	+	Many hypertrophic adenomas
25	1927	37 M	Marked atrophy, 0.9 and 1.2 Gm.; dark brown	Advanced atrophy	..	Approximately 10 per cent cortex and medulla
26	1927	32 M	Enlarged, 12 and 18 Gm.; both typical necrosis	Advanced tuberculosis, proliferative type	+	A few hypertrophic adenomas
27	1928	46 M	Both enlarged, typical necrosis	Advanced tuberculosis, necrotic type	+	A few small islands of cortex; a few hypertrophic adenomas
28	1929	28 F	Left large, 26 Gm.; typical necrosis; right small, 10 Gm.; necrosis and fibrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few small islands of cortex; several hypertrophic adenomas

## MATERIAL FOR STUDY

In the past eighteen years, at the Mayo Clinic, necropsies have been performed in twenty-eight cases in which the clinical syndrome of Addison's disease had been present. In 1925, Rowntree<sup>17</sup> briefly commented on eight of these cases with regard to the observations at necropsy. A review of the protocols and reexamination of all the material available from these twenty-eight necropsies form the basis for this study.

A summary of the condition of the suprarenal glands in these twenty-eight cases is given in table 1. The typical brownish pigmentation of the skin was seen in all of these cases at the time of necropsy except in cases 13 and 22. In case 13 pigmentation had been present previously but at the last admission of the patient it apparently had cleared up entirely. In case 22 pigmentation never had been present. The case was reported by Ghrist and Rowntree<sup>18</sup> in 1927.

## LESIONS OF THE SUPRARENAL GLANDS

*Tuberculosis.*—In twenty-five of the twenty-eight cases, there was a lesion of the suprarenal glands which on histologic examination was called tuberculosis. In the sections of all of these, there were typical

17. Rowntree, L. G.: Studies in Addison's Disease, J. A. M. A. **84**:327 (Jan. 31) 1925.

18. Ghrist, D. G., and Rowntree, L. G.: Addison's Disease Without Pigmentation: Report of a Case, Endocrinology **2**:589, 1927.

areas consisting of tubercles with endothelioid cells, giant cells, fibroblasts and lymphocytes. Since the absolute diagnosis of tuberculosis rests on the observation of the bacilli in the lesions, or in material obtained from the lesions, sections 5 microns thick cut from nineteen of the tuberculous suprarenal glands were stained with the Ziehl-Neelsen stain. Acid-fast bacilli morphologically resembling bacilli of tuberculosis were found in these sections in eleven cases. It will be noted that in the material from necropsies in 1925, or later, bacilli of tuberculosis were found in eleven of fourteen cases, and that they were not found in the material from any of the necropsies before 1925.

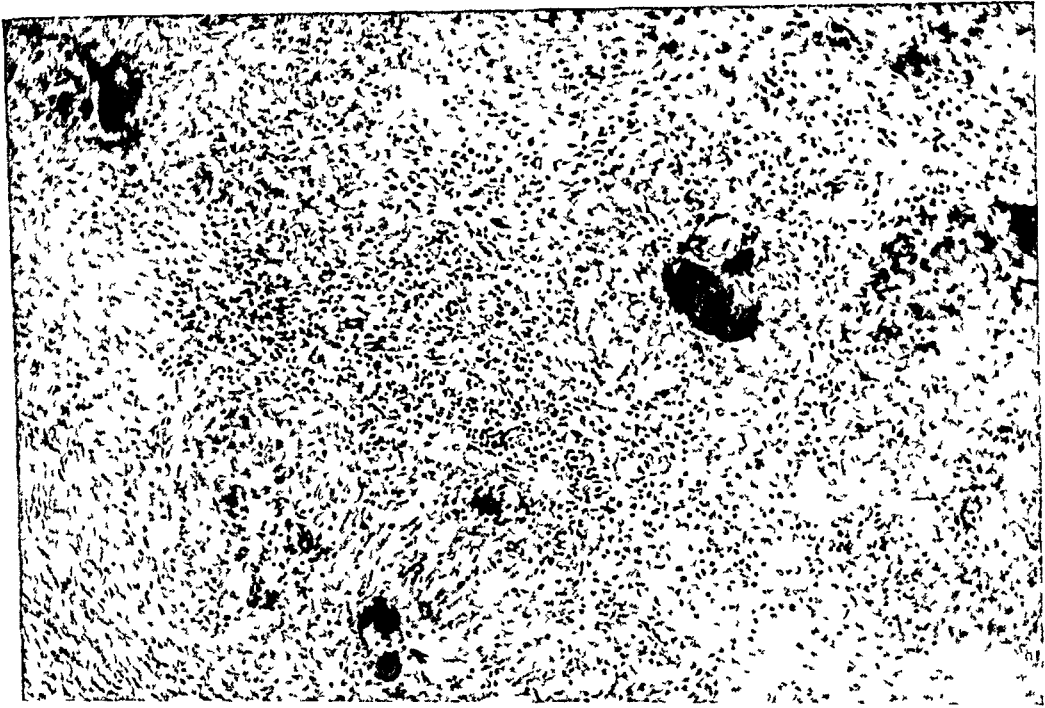


Fig 1—Tuberculosis of the suprarenal gland, of the active proliferative type,  $\times 150$

A possible explanation for this may be the fact that the tissue from which the sections were cut had been in a diluted solution of formaldehyde, U. S. P. (1:10) for more than four years, and it is thought that with fresh tissue the percentage would be considerably higher. The bacilli were found in areas of necrosis, especially near their margins, and not in the tubercles, giant cells or endothelioid cells.

In considering the histologic appearance of sections from these glands, the tuberculosis was found to be bilateral in all the twenty-five cases and involved the entire gland, with almost complete destruction. The type of lesion varied between two extremes, a very proliferative type with many tubercles, many fibroblasts and connective tissue cells



and only small areas of necrosis (fig. 1), and a type in which the gland was a mass of necrosis surrounded by a fibrous capsule in which there were only a few tubercles and a small number of lymphocytes (fig. 2).

The necrosis consisted of a homogeneous mass that took the eosin stain, and in which there were occasionally fine particles of calcium and often fat droplets near the margins. Grossly, the necrosis differed from the ordinary caseous necrosis of tuberculosis in that the necrotic process was yellow or yellowish gray, firm and rubbery and on section presented a uniform surface. This gross picture is well known to pathologists as being characteristic of Addison's disease and differing from most tuberculous necrosis found in other parts of the body. Gross sections of the glands in the more active proliferative types were more or less mottled and apparently nodular, and were more of a pink or pinkish brown than sections from the glands in the less active cases. As a rule, the glands were found to be definitely enlarged. The largest pair weighed 27 and 28 Gm., respectively, compared with a normal weight of from 4 to 10 Gm. In some cases one tuberculous gland was large and the other was normal in size. The glands were not smaller than normal in any case. In only one case (case 17) was there any gross calcification. In this case both suprarenal glands were slightly larger than normal, and about half the substance was replaced by calcium salts.

A definite line of distinction cannot be made among the different types of tuberculous lesions in the suprarenal glands. Of the twenty-five cases in which there were tuberculous lesions in this series, the lesions were essentially proliferative, with many tubercles and little necrosis, in seven cases; proliferative and necrotic, with a moderate number of tubercles and moderate necrosis, in eight cases; essentially necrotic, with extensive encapsulated necrosis with few tubercles, in eight cases, and inactive, accompanied by encapsulated necrosis, with or without calcium deposits, and a few foci of lymphocytes, in two cases.

Certain other observers have stated that the suprarenal glands were completely destroyed by the tuberculous process. Whenever possible, numerous sections of the glands were examined to determine whether any suprarenal tissue remained. It is notable that some cortical tissue was found in twenty-four of the twenty-five cases. In the one case in which it was not found only one section from each gland was available for study, so the data may be considered incomplete. The remaining suprarenal tissue was seen only as small islands of cortex near the periphery (fig. 3) or as cortical adenomas near or beyond the margin of the tuberculous process (fig. 4). The remaining suprarenal cells were usually hypertrophic and moderately hyperchromatic. The nuclei were large and deeply staining and usually there was a brown pigment, probably melanin, uniformly distributed through the cytoplasm. The amount

of this suprarenal cortical tissue was always very small when compared with the total amount in a normal adult and was estimated at less than 5 per cent of the normal amount.

In only one case was any of the medulla of the suprarenal glands seen, and in this case the amount was in a small area. This case, however, was the only one of the series in which there was no pigmentation.

In order to have some conception of the method of development of suprarenal tuberculosis, eight cases were studied in which there were early tuberculous lesions. In none of these cases were there clinical symptoms of Addison's disease. In four cases, the process involved only one suprarenal gland and in four, both glands. In three of these

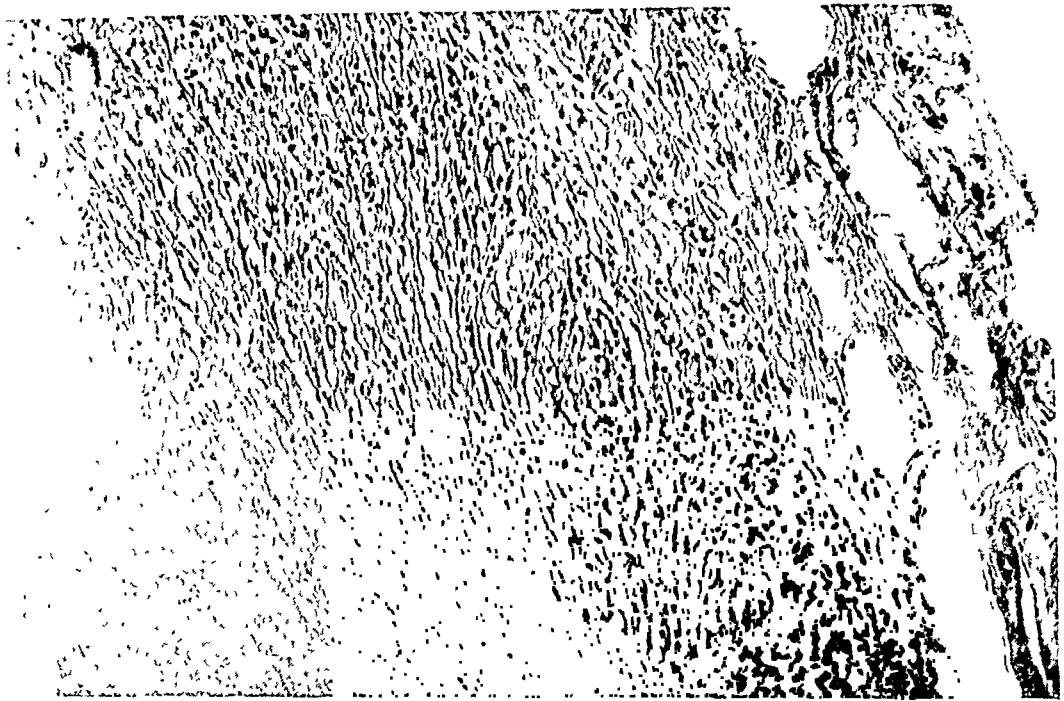


Fig. 2.—Advanced tuberculosis of the suprarenal gland, of the encapsulated necrotic type;  $\times 150$ .

eight cases there was associated generalized miliary tuberculosis; in two, renal tuberculosis; in one case tuberculous spondylitis, and in two cases there were healed tuberculous lesions in other parts of the body but other active foci were not found. The maximal amount of suprarenal destruction was approximately 80 per cent of both glands in the case of tuberculous spondylitis. In the others, more than 50 per cent of normal suprarenal tissue remained.

The lesions in these early cases were situated rather consistently in two places: either at some distance from the main suprarenal vein in the medulla or in deep layers of the cortex or else midway in the cortex between the medulla and the outer surface. The larger lesions

seemed to have spread centrifugally until they extended through practically the full thickness of the gland. The lesions consisted mainly of regions of necrosis which stained deeply with eosin and were surrounded by a rather narrow margin of lymphocytes in which there were a few tubercles and giant cells. There were comparatively few connective tissue fibers or fibroblasts. The lymphocytes extended into the surrounding tissue only for a short distance. Apparently the lesion was spreading without much resistance on the part of the gland.

From the appearance of early and late tuberculous lesions of the suprarenal glands, certain generalizations are suggested. One type of the lesion apparently encounters active resistance and much cellular

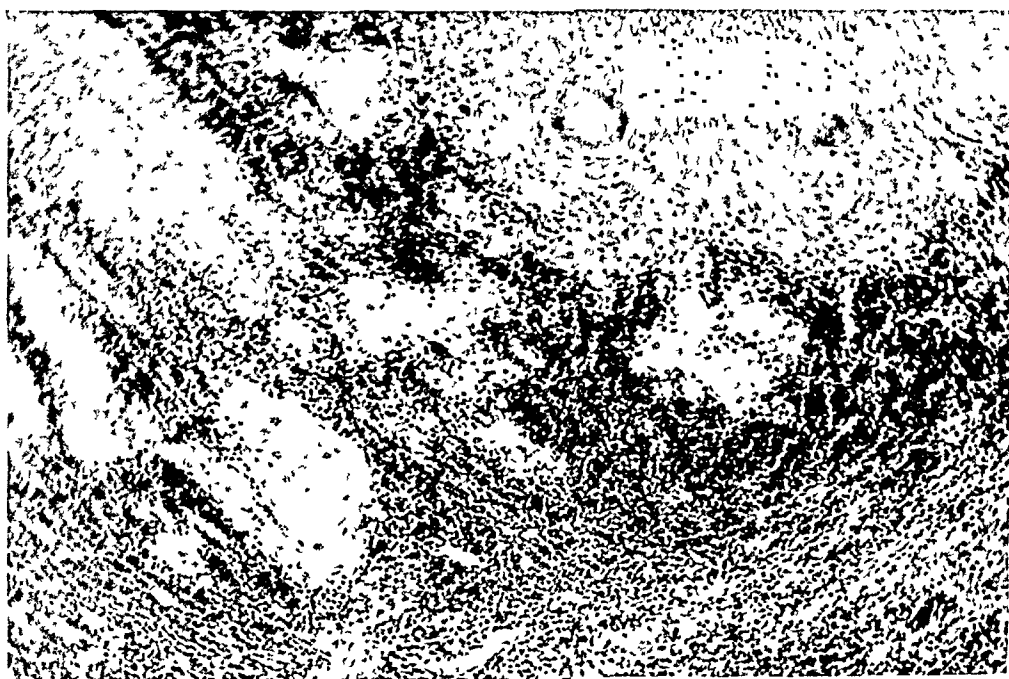


Fig. 3.—Advanced tuberculosis of the suprarenal gland with an island of cortical cells in the inflammatory tissue;  $\times 150$ .

proliferation, which, together with some necrosis, gradually destroys the gland. Another type encounters little resistance; areas of necrosis gradually spread until the gland is practically destroyed, and the necrotic mass becomes encapsulated. Between these two types there are intermediate types.

The process apparently starts in the medulla or midcortical region, and spreads centrifugally. The medulla and the suprarenal veins must be destroyed rather early in the process and the last portions of the gland to be involved are the outer layers of the cortex and any cortical adenomas which may lie beyond. Hence the arterial supply, coming from several vessels which tend to ramify on the surface, is involved

rather late in the process. As the gland nears complete destruction, the remaining cortical cells tend to hypertrophy and become deeply pigmented. It is difficult to determine whether there is an increase in the number of cells in the adenomas or whether there is merely hypertrophy of the cells already present. The type of necrosis is usually peculiar to the organ and may be due to the blood supply or to the lipoid and melanin content of the gland. From observations on suprarenal glands from approximately 1,000 necropsies at The Mayo Clinic small areas of healed tuberculous lesions, such as those which are found in the lungs, liver and spleen, have not been found in the suprarenal glands. Robertson,<sup>19</sup> with a much larger experience in necropsy

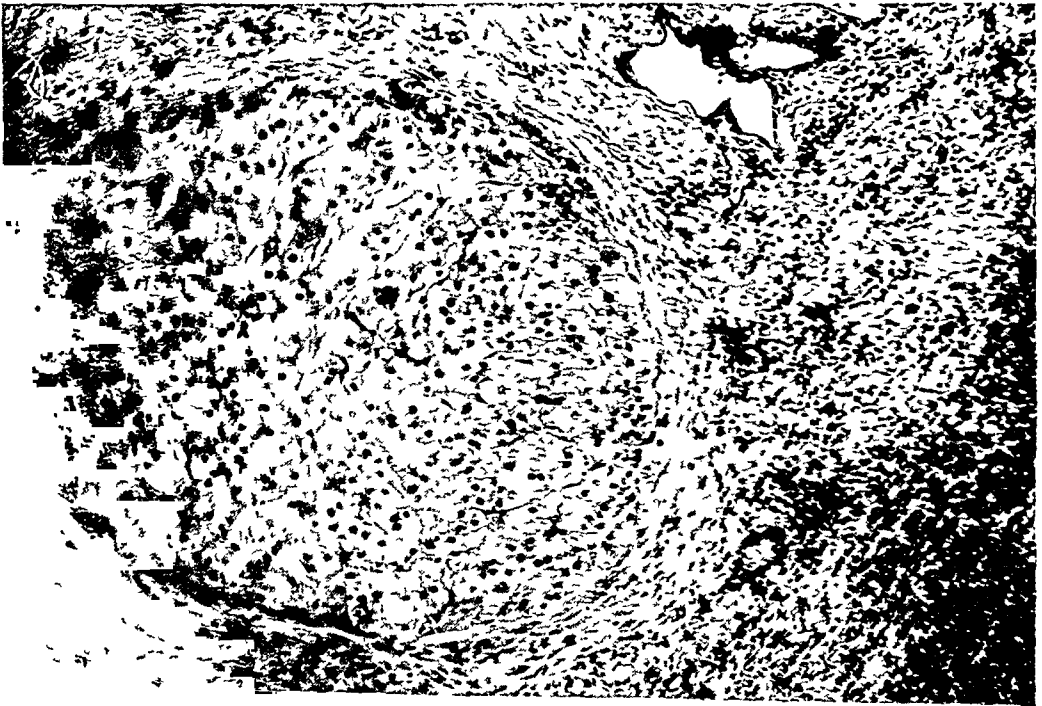


Fig. 4—Advanced tuberculosis of the suprarenal gland with hypertrophic cortical adenoma remaining,  $\times 150$

work, stated that he had never seen evidence of healed tuberculous lesions in the suprarenal glands. It would appear that the tuberculous process is always progressive until the gland is almost completely destroyed.

*Atrophy.*—The remaining three of the twenty-eight cases of Addison's disease which were studied had advanced atrophy of the suprarenal glands.

In case 9, the glands were similar and were very small. Histologic study of sections of these showed that the medulla was fairly normal

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19. Robertson, H E Personal communication to the author

but that the cortex was reduced to a narrow strip. Under higher magnification the cortex was found to consist of isolated cortical cells and groups of cortical cells; all of these cells were large, deeply stained and pigmented and contained large, dark nuclei which varied much in size. Between the cells were numerous lymphocytes throughout the cortical layers, and on the margins were numerous fibroblasts (fig. 5). The whole gland was surrounded by a rather thick capsule of fibrous tissue. In a few places in the cortex, and in the fat around the cortex, there were areas of recent hemorrhage. This is similar to the condition in Brenner's third case.

The picture was difficult to interpret. There was unquestionably a chronic inflammatory reaction in the suprarenal cortex, and the reaction

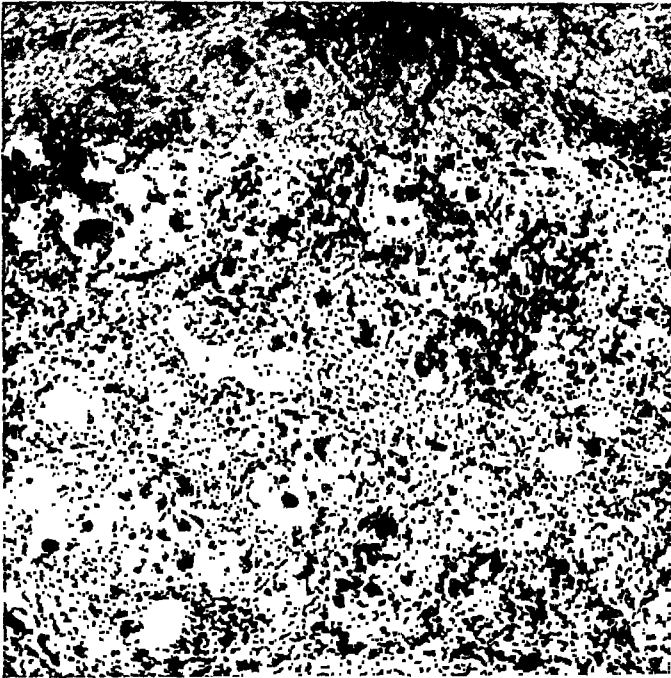


Fig. 5.—Advanced suprarenal atrophy with hypertrophy of the remaining cortical cells and inflammatory reaction of an unknown cause;  $\times 150$ .

was more or less restricted to the cortex. There was no histologic evidence of tuberculosis. The great reduction in the thickness of the cortex, the small number of cells remaining, their isolation and their marked hypertrophy, however, suggest that some toxic agent was destroying the cortical cells and that the inflammatory reaction was provoked by the destroyed cells. That primary hemorrhage had taken place is possible but the diffuseness and bilaterality of the lesion, as well as the absence of blood pigment, are against this. The condition is probably best considered, as Brenner believes, as primary toxic atrophy or as a low grade inflammatory process of unknown cause.

In case 13, one suprarenal gland was found to be a solid calcified mass about the size of a normal gland. The only remains of the other gland were found to be two small nodules of rather dark colored tissue, each about 5 mm. in diameter. Histologically, these consisted of deeply pigmented medullary tissue with a narrow margin of normal size but deeply pigmented cortical cells. The patient in this case had had cutaneous pigmentation but this had cleared up some time before death. Also, this patient had had a positive Wassermann reaction of the blood and a history of syphilis and intensive treatment. The calcified mass may have been tuberculous, but this cannot be proved. The part played by syphilis is doubtful.

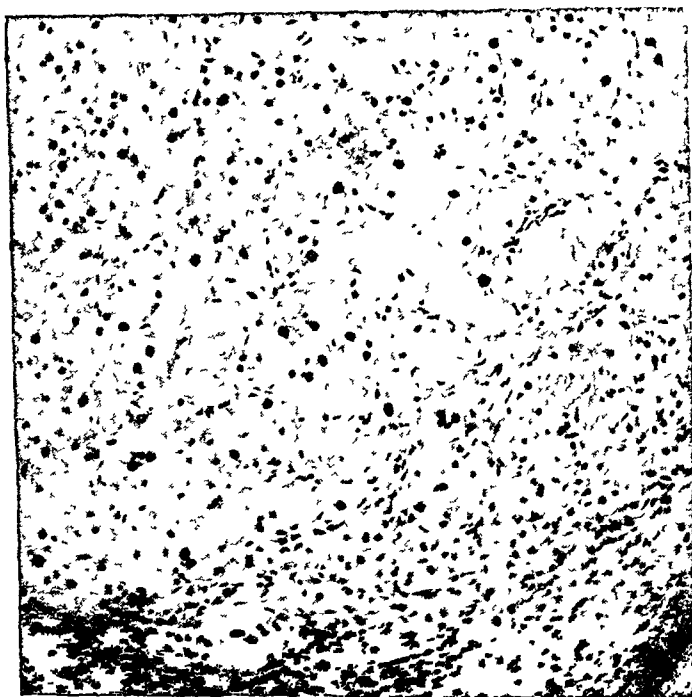


Fig 6.—Advanced suprarenal atrophy with attempts at hypertrophy and regeneration of the cortical cells;  $\times 150$ .

Several cases are reported in the literature in which there was tuberculous destruction of one suprarenal gland and atrophy of the other. One possible explanation of the sequence of events in case 13 is that several years before death one suprarenal gland had been destroyed and had become calcified without any addisonian symptoms being manifest. Then active syphilis or some other toxic process had caused atrophy of the other suprarenal gland and pigmentation had developed. The atrophy was then arrested either spontaneously or by antisiphilitic treatment; the remnant of the atrophied gland regenerated, and the pigmentation disappeared.

In case 25, the two glands were similar. They were dark brown, nodular and weighed 0.9 and 1.2 Gm., respectively. Histologic study of sections revealed marked diminution in the amount of both cortex and medulla; the latter apparently had been more affected. The cortex was composed mostly of nodules, which under low power magnification resembled a cluster of cortical adenomas. Under higher magnification, marked alterations in the cortical cells were observed. These varied tremendously in size; many were very large, with poorly staining cytoplasm, in which there was a moderate amount of pale brown pigment. The nuclei also varied in size and stained deeply. The cells were not arranged in any discernible order. The general appearance suggested that there was a striking reduction in the number of cortical cells and that those remaining had undergone compensatory hypertrophy (fig. 6). There was no evidence of any acute or chronic inflammatory process in either gland. This condition corresponds to that of the suprarenal glands in the case reported by Kiefer.

#### LESIONS OTHER THAN THOSE OF THE SUPRARENAL GLANDS

Although the syndrome of Addison's disease has long been associated with extensive lesions of the suprarenal glands, changes in other organs should not be neglected, and I have tried so far as possible to secure and tabulate all the available necropsy data on the twenty-eight cases presented in order to determine what other lesions were present often enough to appear significant.

*Active Tuberculous Lesions.*—One of the first questions that arises in cases of suprarenal tuberculosis is concerned with the association of healed or active tuberculous lesions of other parts of the body; the answer to this question might throw some light on the portal of entry and the question of specificity of the organisms. Other writers on the subject frequently have found both healed and active lesions of other organs associated with Addison's disease. In all of the twenty-five cases of tuberculosis of the suprarenal glands in this series there were lesions that were considered to be those of healed pulmonary tuberculosis; these consisted of calcified nodules in the lungs and lymph nodes of the hilum, and pleural adhesions. In all there were at least two of these three types. In addition, in six cases were what appeared to be healed lesions of tuberculosis in at least one of the following sites: the spleen, the liver, the peritoneum and the joints. It is well known that the incidence of healed pulmonary tuberculosis is high, as determined by the routine of necropsy examinations, but that it is rarely as high as 100 per cent in any group of twenty-five cases. In one of the three cases in which there was atrophy of the suprarenal glands (case 25) a demonstrable healed or active tuberculous process was not found. Data concerning active tuberculosis are given in table 2.

TABLE 2.—Summary of Pathologic Anatomy of Organs Other Than Suprarenal Glands

TABLE 2.—Summary of Pathologic Anatomy																
Case	Active Tuberculous Lesions Other Than Those of the Suprarenal Glands	Body Weight		At Necropsy	Weight of Heart			Condition of Kidneys	Thymus, Nodes, Grade		Hyperplasia					
		Pounds	Kg.		Minimal	Average	Normal Maximal		Grade	Grade	Lymph Nodes, Grade	Intestinal Lymphoid Tissue				
1	Miliary of liver.....	...	...	...	...	...	...	Normal.....	?	?	?	?	Appendix, graded 2			
2	Apexes of both lungs.....	...	...	...	...	...	...	Moderate congestion.....	?	?	?	?	?			
3	Left lung and nodes of hilum.....	105	47	188	165	205	241	Chronic pyelonephritis..	?	?	?	?	?			
4	Miliary of liver and spleen.....	...	...	...	...	...	...	Normal.....	?	?	?	?	?			
5	Abdominal lymph nodes.....	140	63	240	211	253	295	Diffuse tubular atrophy	?	?	?	?	?	Ileum, graded 2		
6	Right lung; right tuberculous empyema..	129	54	300	160	235	276	Diffuse tubular atrophy	?	?	?	?	?	Jejunum, ileum and colon, graded 2		
7	Mesenteric lymph nodes.....	...	...	...	...	...	...	Moderate congestion....	3	3	2	2	2			
8	Both lungs; both kidneys; prostate; left testis; epididymis and seminal vesicles; rectum; miliary of spleen, and abdominal lymph nodes.....	152	69	283	240	300	350	Bilateral tuberculosis....	2	2	2	2	2			
9	None found.....	...	...	...	...	...	...	Marked congestion.....	2	2	2	2	2	Jejunum, ileum, colon and appendix, graded 2		
10	Both lungs and lymph nodes of hilum; miliary of myocardium, abdominal lymph nodes and spleen.....	150	68	211	237	294	345	Diffuse tubular atrophy and marked congestion	2	2	2	2	2	Ileum and jejunum, graded 2		
11	Both lungs; prostate; left testis and epididymis; first and second lumbar vertebrae.....	105	47	189	165	205	241	Moderate congestion....	2	2	2	2	2	Colon, graded 2		
12	Abdominal lymph nodes.....	140	63	297	221	274	322	Diffuse tubular atrophy	1	1	2	2	2	Colon, graded 2		
13	None found.....	150	68	238	237	291	345	Diffuse tubular atrophy and moderate congestion	1	1	2	2	2	Duodenum, ileum and colon, graded 2		
14	Left kidney; spleen; abdominal lymph nodes.....	145	65	310	229	284	333	Left tuberculosis; right normal.....	1	1	2	2	2	Appendix, graded 2		
15	Both lungs (small nodules).....	185	83	292	206	363	382	Chronic pyelonephritis..	2	2	2	2	2	Cecum, graded 2		
16	Right lung (small nodules).....	170	77	205	255	306	343	Diffuse tubular atrophy	2	2	2	2	2	Jejunum and ileum, graded 2		
17	None found.....	91	41	152	136	161	195	Right tuberculosis; left normal.....	1	1	2	2	2			
18	Right kidney; prostate; epididymis; seminal vesicles, abdominal lymph nodes.....	170	77	345	238	333	371	Right tuberculosis; left normal.....	2	2	2	2	2			
19	Both kidneys; prostate; abdominal lymph nodes.....	...	...	...	...	...	...	Bilateral tuberculosis....	2	2	2	2	2			
20	None found.....	161	73	235	254	314	369	Normal.....	?	?	?	?	?			
21	Prostate; left epididymis; left axillary lymph nodes.....	...	...	...	...	...	...	Moderate congestion....	2	2	2	2	2			
22	None found.....	...	...	...	...	...	...	Diffuse tubular atrophy and moderate congestion	?	?	?	?	?			
23	Both lungs.....	135	60	205	213	265	310	Normal.....	2	2	2	2	2	Jejunum, ileum and colon, graded 3		
24	Both lungs; lymph nodes of hilum and trachea.....	143	64	246	225	280	325	Normal.....	3	3	3	3	3			
25	None found.....	133	59	263	210	260	305	Moderate congestion....	3	3	3	3	3			
26	Both lungs (small nodules).....	145	65	220	229	284	333	Normal.....	3	3	3	3	3			
27	Both lungs; pleura; mediastinum; fourth, fifth and sixth thoracic vertebrae; fourth, fifth and sixth right ribs.....	150	68	339	237	294	345	Diffuse tubular atrophy	2	2	2	2	2			
28	Tenth and eleventh thoracic vertebrae with large left psoas abscess; liver.....	120	54	200	180	215	259	Marked diffuse tubular atrophy	2	2	2	2	2	Ileum, graded 2		



Of the twenty-five cases of suprarenal tuberculosis, in ten there was active pulmonary (without genito-urinary) tuberculosis, in four there was active genito-urinary (without pulmonary) tuberculosis, in two there was both active pulmonary and genito-urinary tuberculosis and in one case there was active tuberculosis of the spine without pulmonary or genito-urinary tuberculosis, all of which I believe probably antedated the suprarenal tuberculosis. In three of the remaining eight cases, active tuberculosis of other organs was not found. In the other five cases there was active tuberculosis of the liver, spleen or abdominal lymph nodes, all of which can probably best be considered as coincidental or secondary to the suprarenal tuberculosis. Active tuberculosis was not found in the three cases in which there was atrophy of the suprarenal glands.

*Disproportions Between Cardiac and Body Weight.*—A small heart and small aorta have frequently been described in Addison's disease and have been considered as due to atrophy secondary to the disease itself, particularly to the hypotension and circulatory weakness, or as a part of a sort of congenital status thymicolymphaticus which will be discussed later. In my series there is a record of the weight of the heart in twenty of the twenty-eight cases. With the use of the table of average normal weights of hearts with upper and lower limits as worked out by Smith<sup>20</sup> from total body weights, a comparison of the computed normal weights with the actual weights of the hearts in these twenty cases is given in table 2. The body weights were taken within a few weeks before death, as were Smith's.

The essential facts can best be summarized as follows: The weight of the heart was more than 25 Gm. below the minimal normal in one case, less than 25 Gm. below the minimal normal in six cases, within normal limits but less than the average normal in seven cases, within normal limits but more than the average normal in five cases, and greater than maximal normal in one case; the weight of the heart was thus less than the average normal in fourteen cases and greater than the average normal in six cases.

In this group of twenty cases, all the patients stated as their normal weight a figure higher than that found within a few weeks of their death. The loss in weight varied between 5 and 70 pounds (2.3 and 31.8 Kg.), with an average of 28 pounds (12.7 Kg.). A summary of a comparison of the weights of their hearts at necropsy with the normal weight of the heart in each case as computed from their normal body weight by the method described is as follows: The weight of the heart was more than 25 Gm. below the minimal normal in seven cases, less than 25 Gm. below the minimal normal in four cases, within normal

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20. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am. Heart J.* 4:79, 1928.

limits but less than the average normal in seven cases, and within normal limits but more than average normal in two cases; the weight of the heart was thus less than the average normal in eighteen cases and greater than the average normal in two cases. The significance of the calculations just enumerated is questionable since a certain amount of atrophy of the heart may be expected from a loss of weight due to any cause.

Significant changes were not noted in the size of the aorta in this series except that the circumference at the valve and in the ascending aorta was roughly proportional to the weight of the heart.

*Renal Lesions.*—The frequent presence of albuminuria and terminal renal insufficiency in cases of Addison's disease has raised the question as to whether there is a diffuse renal lesion. In table 2 are given the observations relating to the condition of the kidneys in the series. The essential facts displayed in table 2 in regard to the condition of the kidney are as follows: The kidneys were normal in seven cases, congestion was present in six cases, diffuse tubular atrophy in six cases, congestion and diffuse tubular atrophy in three cases, chronic pyelonephritis in two cases and renal tuberculosis in four cases.

The tubular atrophy mentioned consisted in a flattening out of the epithelial cells, with definite diminution in the amount of cytoplasm. In most of these cases the tubules appeared small in diameter and there was intertubular edema. In several of the cases there was fat in the tubular cells. This picture is interpreted as that of a definite degenerative renal lesion or toxic nephrosis, and its presence in nearly a third of the cases seems significant. It is possible that it is the result of low blood pressure and anoxemia or that it is the result of the peculiar terminal toxemia, the mechanism of which is as yet poorly understood.

*Hyperplasia of Lymphoid Tissue.*—The question of status thymicolymphaticus as a predisposing factor or as a concomitant manifestation in Addison's disease, especially in the cases of atrophy of the suprarenal glands, has been discussed by other authors. In addition to cases in which small hearts were found, a number of cases have been described in which the thymus and lymph nodes were enlarged and in which there was hyperplasia of the lymphoid elements in the small and large intestines. A summary of these data in my series is presented in table 2.

It will be noted that in all three cases of suprarenal atrophy enlargement of the thymus and intestinal lymphoid tissues had taken place. There was a similar condition in seven of the cases of suprarenal tuberculosis and there were varying degrees of lymphoid hyperplasia in a number of the others. An active tuberculous focus as a cause of diffuse lymphoid hyperplasia cannot be ruled out. Certainly, the incidence of these lesions is high in Addison's disease. The spleen was enlarged

in eight cases; its weight varied from 285 to 470 Gm. The enlargement is of doubtful significance.

*Miscellaneous Lesions.*—Other lesions which probably were incidental or which are difficult to link up with Addison's disease were as follows: cholelithiasis in five cases, duodenal ulcer in four cases, melanosis coli in three cases, hyperplasia of Brunner's glands in two cases, carcinoma of the stomach in one case and carcinoma of the rectum in one case.

COMMENT

Because of the reports in the literature of cases of Addison's disease in which the suprarenal glands presented other lesions than tuberculosis

TABLE 3.—*Summary of Lesions of the Suprarenal Glands in Seventy-Three Cases in which Addison's Disease was not Present Clinically.\**

Suprarenal Lesions	Cases	Unilateral Involvement		Bilateral Involvement		Primary Disease
		Estimated Suprarenal Tissue Remaining		Estimated Suprarenal Tissue Remaining		
		per Cent	per Cent	per Cent	per Cent	
Primary carcinoma.....	9	75	50	2	25	10 Carcinoma of suprarenal gland
Primary neurocytoma...	2	50	50	..	..	.. Neurocytoma of suprarenal gland
Primary neuroblastoma	.	.	..	1	15	.. Neuroblastoma of suprarenal gland
Primary paraganglio-neuroma	1	50	..	..	..	.. Paraganglioneuroma of suprarenal gland
Sarcomatous invasion...	1	90	..	..	..	.. Retroperitoneal myxosarcoma
Metastatic sarcoma.....	3	90	50	2	50	25 Sarcoma of various organs
Metastatic carcinoma...	17	90	50	16	90	10 Carcinoma of various organs
Moderate atrophy.....	..	..	..	2	50	50 Pituitary tumor and exophthalmic goiter, respectively
Amyloidosis.....	..	..	..	3	60	15 Pulmonary tuberculosis, osteomyelitis of leg and perinephritic abscess, respectively
Infarction.....	1	50	..	1	20	.. Cardiac disease
Hemorrhage.....	..	..	..	3	50	25 Appendicitis, lobar pneumonia and chronic bronchitis, respectively
Abscess.....	..	..	..	1	25	.. Carcinoma of bladder
Tuberculosis.....	4	80	50	1	90	20 Miliary tuberculosis (3 cases); renal tuberculosis (2 cases); cardiac disease (2 cases); spinal tuberculosis (1 case)

\* In only ten cases was more than 75 per cent of the suprarenal tissue apparently destroyed.

and atrophy, a study was made of all the suprarenal lesions found at necropsy at The Mayo Clinic during the last eighteen years. None of the patients in these cases had clinical Addison's disease. A brief summary of these cases is given in table 3; the group of seventy-three cases includes two cases of moderate atrophy and the eight cases of early or unilateral tuberculosis, previously mentioned, in which the clinical addisonian syndrome was not observed.

It will be noted that the minimal approximate amount of suprarenal tissue remaining was 10 per cent. This is interesting since in only one of the cases of tuberculosis with Addison's syndrome (case 12, table 1) apparently as much as 10 per cent of suprarenal tissue remained; in the other cases there was considerably less than this. It has been suggested by others, however, that an inflammatory lesion is much more likely to produce the clinical syndrome than one that is neoplastic. In one case of tuberculosis the amount of destruction was approximately 80 per cent and addisonian symptoms were not present. If it is considered that suprarenal insufficiency is the cause of Addison's disease it would appear that the limit of the margin of safety is reached when somewhere between 80 and 90 per cent of the suprarenal tissue has been destroyed.

Possibly the reasons why neoplastic lesions produce Addison's disease so rarely are that the patient rarely lives long enough to have tumors in both glands and if he does the primary disease or metastasis to other vital organs causes death before the suprarenal tumors have grown large enough to destroy much suprarenal tissue. It is evident that although malignant tumors are invasive, they are not nearly so destructive to highly specialized glandular tissue as is tuberculosis. Amyloidosis as a destructive agent may be considered as acting more like malignant conditions than like tuberculosis. The cases of infarction, hemorrhage and abscess in table 3 apparently were associated with terminal stages of the primary disease. Records of cases of gumma or fatty replacement of the suprarenal glands were not found in the material studied.

#### SUMMARY

Necropsy data are presented from twenty-eight cases of Addison's disease. Among these, there was bilateral tuberculosis of the suprarenal glands in twenty-five; acid-fast bacilli were demonstrated in eleven of these cases. There was advanced bilateral suprarenal atrophy in three cases. In all the cases but one some suprarenal tissue remained; the maximal amount remaining in any one case was approximately 10 per cent of the normal.

Healed tuberculous lesions of the lungs were found in all the cases in which there was tuberculosis of the suprarenal glands. Active tuberculosis of other organs was found in twenty-two of these. The weight of the heart was less than the average normal in fourteen of twenty cases in which data on the weight of the heart were available. Diffuse degenerative changes in the renal tubules were present in nine cases. In ten cases, including the three cases of suprarenal atrophy, the thymus was enlarged and there was hyperplasia of lymphoid tissue in the nodes and intestinal tract. There was scattered lymphoid hyperplasia in eight other cases.

Seventy-three cases in which there were suprarenal lesions but in which clinical evidence of Addison's disease was lacking are briefly presented. Among these seventy-three cases are included the following: primary suprarenal neoplasms, fifteen cases; secondary suprarenal neoplasms, thirty-nine cases; atrophy, two cases; amyloidosis, three cases; infarction, two cases; hemorrhage, three cases; abscess, one case, and tuberculosis, eight cases.

# LATE GROSS LESIONS IN THE AORTA AND PULMONARY ARTERY FOLLOWING RHEUMATIC FEVER\*

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The fact that widespread lesions commonly occur in the aorta and the vessels throughout the body during and following rheumatic fever has been definitely established by Pappenheimer and von Glahn<sup>1</sup> in their important extension of the earlier observations of Klotz.<sup>2</sup> Since their publication, numerous observers<sup>3</sup> have added valuable confirmatory data. In almost every instance, however, the vascular lesions described have been microscopic. Recently Kugel and Epstein<sup>4</sup> and Perla and Deutsch<sup>5</sup> have called attention to the gross changes that may occur in acute rheumatic fever in the aorta and the pulmonary artery; Pappenheimer and von Glahn<sup>6</sup> also reported the presence of brownish plaques in one of their cases. We believe that late gross lesions may occur and readily be explained by the occurrence and confluence in a localized area of the small flame-shaped scars which are the microscopic changes characteristically found in the media. We have recently had the opportunity to examine an aneurysm of the aorta in which all the evidence pointed to a rheumatic origin and a pathologic process of this type. This case, which we shall report, prompted us to examine all the hearts available in our laboratory for evidence of gross lesions intermediary between the microscopic scars and the formation of an aneurysm. Unfortunately, few specimens of the aorta, except for limited portions attached to the heart, had been preserved. It is the purpose of this

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\* Submitted for publication, April 13, 1929.

\* From the Department of Pathology of Washington University School of Medicine, and of Barnes Hospital.

1. Pappenheimer, A. M., and von Glahn, W. C.: *J. M. Research* **44**:489, 1924; *Am. J. Path.* **2**:15 and 235, 1926; *ibid.* **3**:583, 1927.

2. Klotz, O.: *Tr. A. Am. Phys.* **27**:181, 1912.

3. Paul, J. R.: *Medicine* **7**:383, 1928. Kugel, M. A., and Epstein, E. Z.: *Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease*, *Arch. Path.* **6**:247 (Aug.) 1928. Chiari, H.: *Beitr. z. path. Anat. u. z. allg. Path.* **80**:336, 1928. Perla, D., and Deutsch, M.: *Am. J. Path.* **5**:45, 1929.

4. Kugel and Epstein (footnote 3, second reference).

5. Perla and Deutsch (footnote 3, fourth reference).

6. Pappenheimer and von Glahn (footnote 1, third reference).

paper to report the late gross lesions that were discovered in the aorta and pulmonary artery of the rheumatic hearts examined, and to correlate such lesions, as far as possible, with the known pathologic changes in rheumatic fever. In doing so, we make the reservation, however, that what we know as rheumatic fever awaits the accepted discovery of the causative agent of this disease and the experimental production of its lesions.

In selecting the material, the criteria of Pappenheimer and von Glahn were adopted, namely: (1) a clinical history of one or more attacks of rheumatic fever or of chorea or of repeated attacks of tonsillitis; (2) the presence of the typical lesions of rheumatic fever in the heart, and (3) the absence of syphilis in the history, in the serologic reaction and in the gross or histologic appearance of the aorta and the other organs. In addition, arteriosclerosis and known mycotic processes were considered and ruled out in each case. Three cases besides the one in which aneurysm was shown were found that conformed to these conditions, although three or four others might have been included in this number. Only the essential details will be given in the descriptions of the cases.

#### REPORT OF CASES

**CASE 1.**—J. H., a white woman, aged 20, entered Barnes Hospital with heart failure and auricular fibrillation. She gave a history of repeated attacks of tonsillitis and rheumatic fever with arthritis. The Wassermann reaction was negative. The blood pressure was 140 systolic and 85 diastolic. The autopsy, which was limited to the chest, revealed an enlarged heart and chronic tricuspid and mitral endocarditis; the mitral valve being of button-hole type. Six fine, smooth depressions about 1 mm. in diameter gave the pulmonary artery, in an area 3 cm. above its origin, a honeycomb appearance (fig. 1). On section, the intima between the depressions appeared thickened and the media somewhat irregular. The adventitia was wider than normal, containing numerous vessels.

*Microscopic Examination.*—The intima of the pulmonary artery in places was over one-half as thick as the media (fig. 2). This thickening was produced by an increase in connective tissue, the intima near the lumen being dense and hyaline, and that near the media being more cellular. Only an occasional lymphocyte was seen. The muscle of the media, in a few places, especially beneath the depressions, had disappeared, and its place had been taken by connective tissue (fig. 2). A van Gieson stain for elastic tissue revealed a frayed and slightly broken elastic layer, which in places was pushed aside by small bands of connective tissue. The arteries and veins of the adventitia were thickened, the latter eccentrically.

The small arteries and arterioles of the myocardium, pericardium, auricle, aorta and lung were definitely thickened by hyaline connective tissue.

**CASE 2.**—J. S., aged 40, a white man, had rheumatic fever at the ages of 12, 22 and 32. The Wassermann reaction was negative on two occasions. The blood pressure was 160 systolic and 120 diastolic. No scar was seen on the penis. Death was caused in this case by heart failure. At postmortem examination, the heart was found to weigh 510 Gm. The mitral valve was stenosed; the aortic and tricuspid valves were definitely fibrosed. The mouth of the left coronary



Fig. 1 (case 1).—Pulmonary artery, showing gross scarring;  $\times 2$ .

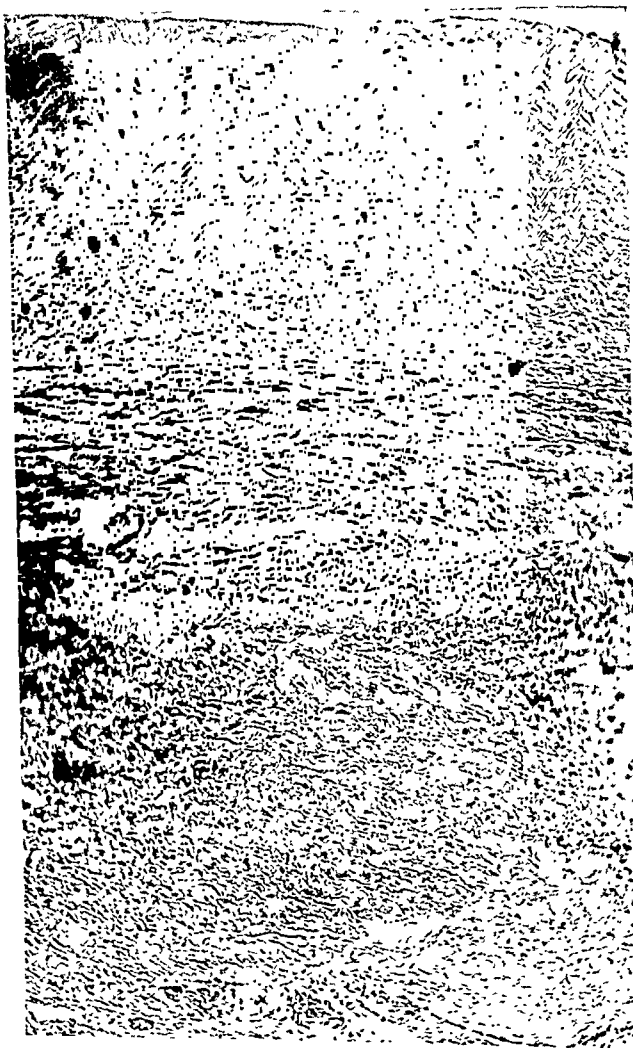


Fig. 2 (case 1).—Hypertrophy of intima. Disappearance of the muscle of media and replacement with scar tissue;  $\times 85$ .





Fig. 3 (case 2).—Scarring of the mouth of the coronary artery.

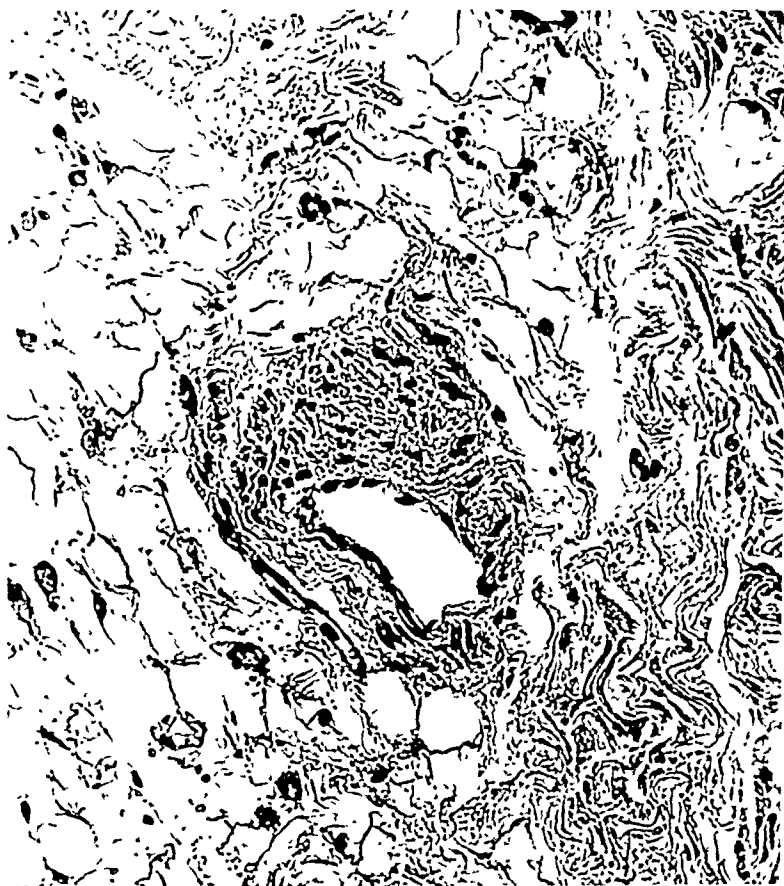


Fig. 4 (case 2).—Eccentric fibrous thickening of veins. A similar picture was seen in veins in all cases;  $\times 250$ .

artery was widened, especially on its mesial aspect, where several small scars (fig. 3) gave the opening of the coronary artery a puckered appearance.

*Microscopic Examination.*—The intima was moderately thickened and contained a small calcified area. The media was partially broken by several scars, some of which had attained a fair size. The adventitia showed changes that were found in all the cases: increase in connective tissue, chiefly hyaline; thickening of the small arteries and arterioles, and eccentric thickening of the veins (fig. 4).

The connective tissue was increased about the vessels of the myocardium. There were several small scars that showed no definite perivascular arrangement. The small arteries and arterioles of the kidneys, intestines, prostate, spleen and suprarenal glands were thickened.



Fig. 5 (case 3).—Large scar in upper part of aorta. Stippled appearance in lower part of aorta caused by numerous small scars in media.

CASE 3.—J. G., a white man, aged 47, entered Barnes Hospital with all the signs and symptoms of heart failure. He denied having had any childhood disease, rheumatic fever, chorea or syphilis. He had always been susceptible to colds. He had had "water on the chest" at varying intervals since he was 7 years old. The physical examination revealed ragged, scarred tonsils, aortic insufficiency and mitral stenosis. The Wassermann reaction was negative on three occasions. The blood pressure was 120 systolic and 80 diastolic. No scar was found on the penis.

Grossly, the aorta, 8 cm. above the aortic valve, showed a linear scar about 1.5 cm. in length, with a smooth, thickened intima surrounding it (fig. 5). On section, the media was found to be decreased in the region of the depression; the

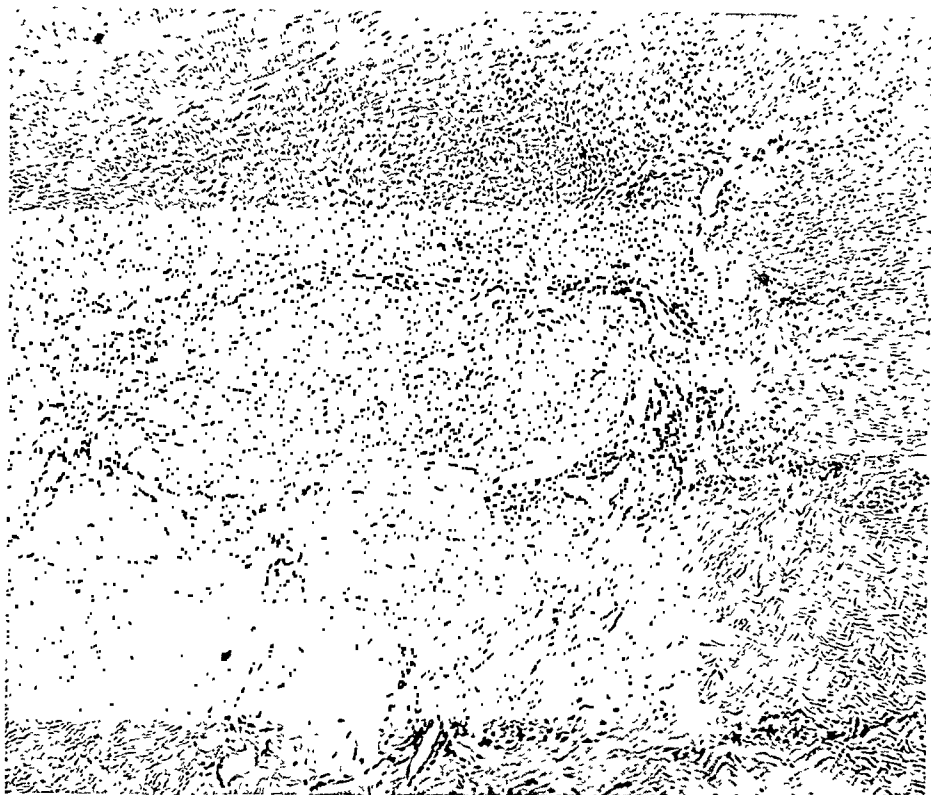


Fig. 6 (case 3).—Scar in media, showing destruction of media. Slight cellular reaction;  $\times 85$ .

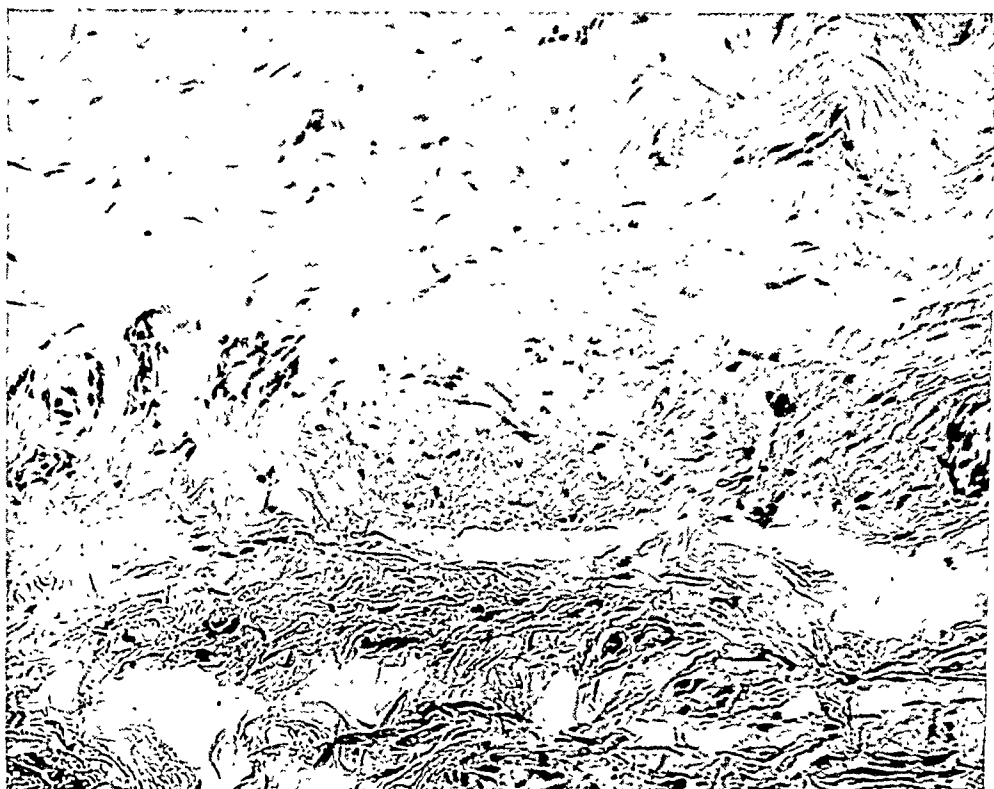


Fig. 7 (case 3).—Fibrous thickening of small artery;  $\times 213$ .

intima and adventitia were thickened. Immediately above the aortic valve, the intima of the aorta was given a stippled appearance by numerous fine depressions. On section, the intima was seen to be irregularly thickened; the media was found to contain many small red points. The aortic and mitral valves were markedly fibrosed, the latter valve presenting a mere slit as its opening. The heart was enlarged.

*Microscopic Examination.*—The media tapered down to a thin layer at the site of the large gross scar, whereas the intima and adventitia were considerably thickened. The numerous scars in the media are illustrated in figure 6. The muscle and elastic tissues were broken by the vascularized connective tissue, in which only occasional lymphocytes were noted. The adventitia consisted of a



Fig. 8 (case 3).—Elastic tissue (van Gieson stain), showing scar in media;  $\times 90$ .

broad layer of hyalinized connective tissue, in which many thickened vessels, such as the one illustrated in figure 7, were prominent. The increased thickness of the walls of these vessels was found by a van Gieson stain for elastic tissue to be due to hyaline connective tissue in the media. Several small accumulations of lymphocytes were located in the lowermost portions of the connective tissue. The thickened intima consisted of a somewhat loose connective tissue and a few lymphocytes. This thickening of the intima together with small scars beneath the depressions accounted for the stippled appearance in the lower part of the aorta.

The aorta adjacent to these regions and elsewhere revealed a media that was changed by small scars, figure 8, and an adventitia that was increased in width

by hyaline connective tissue in which were thickened small arteries and arterioles. Many of the small veins of the aorta throughout the various sections of the aorta showed eccentric thickening by either cellular or dense connective tissue (similar to that illustrated in fig. 4).

The perivascular connective tissue of the myocardium was increased. The small arteries and arterioles of the myocardium, pericardium, lungs, liver, pancreas, peripancreatic fat, kidneys, suprarenal glands, prostate and spleen were thickened in a mild degree.



Fig. 9 (case 4).—An aneurysm of the aorta of dissecting type. The small opening of the aneurysm and the smoothness of the aorta may be noted.

CASE 4.—P. F., a white man, aged 39, a salesman, was admitted to Barnes Hospital for dyspnea and marked palpitation of the heart. At the ages of 23 and 25, he had had severe attacks of rheumatic fever with involvement of the joints. He denied having had a chancre. He was married and had two children, who were alive and well. Miscarriages, stillbirths or other signs of syphilis were absent in the history. For the past four years he had been having palpitations, which, he was told, were due to a "leaky heart." Dyspnea had been pronounced for three weeks.

The physical examination revealed an orthopneic and dyspneic person with external cyanosis of the lips and fingers. Cardiac decompensation was evident. Blood culture and Wassermann and Kahn tests of the blood were negative. The

blood pressure was 82 systolic and 68 diastolic. The clinical course was rapidly downhill. The patient died of cardiac failure.

*Autopsy.*—At autopsy, an aneurysm of the aorta was seen above and partially attached to the right auricle, arising from the ascending portion of the arch of the aorta. On section, this aneurysm was found to be unusual (fig. 9). The laminated thrombus of the aneurysm was in communication with the aorta at a point 2 cm. above the aortic valve through a smooth, round opening, 1 cm. in diameter. The main mass, which measured 8 by 7 by 5 cm., was covered posteriorly by the wall of the aorta, which, however, did not consist of more than the intima and about half of the media. The upper angle of the aneurysm



Fig. 10 (case 4) —The upper edge of the aneurysm, showing the dissection of the aorta. Connective tissue binds the two halves of the aorta. Several small scars are seen in the adventitial half of the media. Elastic tissue shown by van Gieson stain.

showed the media split in two so that part of the media was a direct extension of the posterior surface just described, while the other part formed the anterior upper wall of the aneurysm. The remainder of the anterior wall consisted of dense hyaline connective tissue and the adherent right auricle. The aortic wall below the opening did not show this dissecting process. The aneurysm extended down to about the line of attachment of the aortic valve. The intima, except for the opening, was smooth; no scarring was found, and only a few small atheromas were noticed. The cusps of the aortic valve were thick, short and retracted, the anterior and right posterior cusps being fused; and at this point calcium was felt.

Otherwise, the thickening was fibrous. The aorta above the cusps did not show any change. The mitral valve was thickened, especially the anterior leaflet, where a few of the chordae tendineae were shortened and thickened.

*Microscopic Examination.*—Around the opening in the aorta, muscle and elastic tissue were intermingled with connective tissue, which extended into and covered the thrombus for a short distance. In either direction away from the opening, the muscular elastic coat was not broken. The portion of the aorta that formed the posterior wall of the aneurysm consisted of an intima that was increased by connective tissue, and a media that was thin, but contained unbroken muscle and elastic tissue and a layer of fairly cellular connective tissue. This was separated from the thrombotic mass by dense hyaline connective tissue. The split in the media, at the upper angle of the aneurysm, was held together by connective tissue (fig. 10). The portion of the aorta here that still remained as part of the aorta showed no change, that portion which formed the anterior upper surface of the aneurysm was the site of numerous small vascularized scars with a thickened fibrosed adventitia next to it (fig. 10). No lymphocytic reaction was found here. A section through the middle of the anterior surface of the aneurysm at a point farthest away from the aorta revealed a dense layer of hyaline connective tissue and a few strands of broken elastic tissue. The latter was next to the thrombus. The thrombus was undergoing organization only near the aorta itself.

Several sections were taken through the aorta away from the aneurysm, two of them beneath atheromas. One of the sections beneath an atheroma showed a thinned media in which the lower half was partially replaced by several scars. The adventitia at and adjacent to this point was thickened. Throughout the adventitia in all parts of the aorta the arterioles and veins were thickened, the thickening in the latter usually being eccentric. Many arterioles of the heart and an occasional vessel of the other organs showed slight thickening. There were several small scars in the heart situated chiefly about the vessels.

#### COMMENT

These late gross lesions of the aorta and the pulmonary artery can readily be interpreted as the sequelae of previous rheumatic lesions. The excessive intimal thickening that plays so important a rôle in case 1 is the late result of the gross acute lesion that has already been described by Perla and Deutsch. In their paper, figure 7 pictures an intimal change that in extensiveness and time is only slightly removed from the intimal change in case 1.

It is somewhat difficult to decide on the etiologic mechanism in the production of this intimal change. The constant presence of medial change and the widespread involvement of the vessels tend to favor the view that the infective agent is brought by way of the vasa vasorum rather than through the lumen of the aorta or the pulmonary artery. If this is true, we must emphasize the possibility of marked injury to the intima with moderate involvement of the media, the adventitia and the vasa vasorum.

Although in the European literature one reads many accounts of the destructive effects of rheumatic fever on the aorta, few of these

accounts offer definite histologic evidence. Recently Wiesel<sup>7</sup> and Besançon and Weil<sup>8</sup> have emphasized the serious involvement of the aorta. From the known pathologic changes in rheumatic fever and from our studies, we can understand how gross lesions and even the formation of an aneurysm may be the sequelae of rheumatic fever. The mechanism for the production of these lesions may be predicated from the changes that have been found in rheumatic fever and accepted as being due to that disease. Should the acute reaction that is described as the forerunner of the flame-shaped scars be a little more extensive or should several of these lesions be localized in one area, the resulting healing process may well terminate in a gross scar; or should the reaction take place within a wall of the vasa vasorum with a subsequent thrombosis of that vessel, gross scarring may result. We have seen this latter process in its acute stage in the coronary artery and in the branches of the pulmonary artery. We have seen the apex of the heart<sup>9</sup> markedly thinned and slightly bulging in rheumatic fever. This was thought to be due to the late results of a coronary thrombus caused by rheumatic fever. The large scars that we sometimes see in the kidneys and spleen, that resemble healed infarcts, are probably due to thrombosis of the vessels of these organs in patients who have had rheumatic fever. The rarity of these gross lesions in the aorta may be attributed either to the relatively slight involvement of the aorta in rheumatic fever or to the belief that because the scars of the media resemble a process produced by syphilis it is a syphilitic process. Aside from the history, the clinical picture, the serologic tests and the observations in the other parts of the body, there are definite histologic differences between the scars of the media in syphilis and the scars found in these cases that we believe are due to rheumatic fever.

The gross scarring was confined to one small area, except in case 3, in which two localities had undergone change. In none of the regions of the scars did we find more than a few lymphocytes. This fits in well with the late lesions of rheumatic fever in the heart valves and the myocardium, and the descriptions of the aortic lesions by Pappenheimer and von Glahn. It would indeed be unbelievably rare to find four cases in which the Wassermann and Kahn tests were negative, in which there had been no history of or treatment for syphilis and in which there was unquestioned rheumatic involvement, which would show what might be considered an atypical syphilitic aortitis. The changes in the smaller arteries and veins in no instance consisted of the intimal proliferation that one so frequently sees in syphilis. When the vessels were thickened, we usually found an increase in connective tissue within the wall of the

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7. Wiesel, J.: *Med. Klin.* **19**:197, 1923.

8. Besançon, K., and Weil, M. D.: *Lancet* **1**:1002, 1928.

9. McCordock, H. A., to be published.



vessel and not an increase in the intima of the vessel. The eccentric thickening of the veins by connective tissue probably is the late stage of an acute reaction that Chiari<sup>10</sup> described as occurring in rheumatic fever. The increase in connective tissue in the adventitia with little lymphocytic reaction in these cases is not confined to the areas of destruction in the media, but is rather diffuse. This, too, was emphasized by Chiari.

The formation of the aneurysm may be plausibly explained on the basis of the changes in rheumatic fever. The aneurysm appears to be the result of a break in the aorta with a subsequent dissection of the aorta along the lower part of the media. The aorta everywhere else was smooth and showed no gross scars and few atheromas. It was this condition that first drew our attention to the fact that here we had an aneurysm that was obviously not syphilitic nor arteriosclerotic nor mycotic. The rupture through the aorta probably occurred at the site of a localized medial destruction similar to the process that produced the gross lesions in cases 2 and 3. The thickened adventitia and lower part of the media held the aorta intact. The lesions in the outer half of the media, to reason from the work of others and the appearance of the aorta at the upper angle of the aneurysm in this case, offered a line of weak points along which the aortic wall could be dissected by the constant force of the blood. This process must have been somewhat slow, because at the farthest point of dissection the split media was held together by well formed connective tissue which appeared to be resisting the advancement of the blood. The formation of a thrombus and the narrowness of the opening were other factors in the probable slow growth of this aneurysm. We found small scars similar to those described in rheumatic fever in the lower part of the media in other parts of the aorta. The rather large medial scar which was found beneath one of the atheromatous plaques was similar to the lesions seen in the other cases, but as yet was too small to be visible grossly. The atheromatous plaque over the site of the thinning of the media was interpreted as being of the nature of a compensatory thickening. There was nothing in the gross or microscopic studies that even suggested an arteriosclerotic or a known mycotic origin for the aneurysm.

The histories in all cases, except case 3, showed definitely the presence of rheumatism. Case 3 belonged to the small group of patients who showed physical and postmortem signs of rheumatic nature, but who gave no history of involvement of the joints or the heart. One should note with interest that this patient as a child had several attacks of what probably was pleurisy. Paul<sup>11</sup> emphasized the frequency and specificity of pleurisy in rheumatic fever.

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10. Chiari (footnote 3, third reference).

11. Paul (footnote 3, first reference).

It might be worth while to mention briefly that in two of the four cases there was hypertension. Gray and Rabinovitch, in this laboratory, are studying the peripheral vessels in the organs of patients with rheumatic fever to determine whether the hypertension which is not uncommon in this disease might not be due to the change in the vessels which results from rheumatic fever.

In our comment, the term rheumatic fever has been used in the sense that the lesions described were not of syphilitic, arteriosclerotic, degenerative mesaortitis or known mycotic origin; the term rheumatic fever has been used rather in the sense that there is a large group of cases that show pathologic changes which, for the most part, probably had their origin definitely in rheumatic fever.

Future study may reveal that there are different organisms, perhaps similar in nature, that directly or through previous sensitization of certain tissues produce lesions that are similar in appearance.

#### SUMMARY

Four cases are described in which gross lesions of the aorta and pulmonary artery are thought to have been late results of rheumatic changes. These lesions consisted in scarring of the media and thickening of the intima. A false aneurysm of the aorta is described and explained on a rheumatic basis. An eccentric fibrosis of the veins of the adventitia is emphasized as being rheumatic.

We are indebted to Dr. D. P. Ban for the use of the case histories.

# THE RÔLE OF CLASMATOCYTES IN PROTECTION AGAINST THE PNEUMOCOCCUS \*

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In recent years particular emphasis has been placed on the relationship between the reticulo-endothelial system of cells (as defined by Aschoff <sup>1</sup>) and immunity. In the reticulo-endothelial system have been included mononuclears, namely, the monocytes of the blood, the clasmatocytes (histiocytes, tissue macrophages) of the connective tissue, the endothelial cells of the capillaries and the Küpffer cells of the liver. Many have held that mononuclear as well as polymorphonuclear cells are concerned in active phagocytic opposition to certain infectious agents.

The importance of the vascular endothelium in the disposal of bacteria has been emphasized by various workers, among whom are Werigo,<sup>2</sup> Adami, Abbott and Nicholson,<sup>3</sup> Kyes <sup>4</sup> and Nagao.<sup>5</sup> Bull,<sup>6</sup> Hopkins and Parker <sup>7</sup> and Louros and Scheyer <sup>8</sup> observed the disappearance of streptococci from the blood stream of animals and their presence in the organs. Bartlett and Ozaki <sup>9</sup> observed marked phagocytosis of staphylococci in blood cells, in the capillaries of the lungs, liver and spleen, the mononuclears playing an important rôle. In a perfusion experiment, Manwaring and Coe <sup>10</sup> demonstrated the adherence of the pneumococci to the endothelial cells lining the hepatic capillaries. Singer and Adler,<sup>11</sup> Robertson and his collaborators,<sup>12</sup> and Wright,<sup>13</sup> after immunization with pneumococci, noted marked phagocytosis by both polymorpho-

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\* Submitted for publication, April 13, 1929.

\* From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

1. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

2. Werigo: Ann. de l'inst. Pasteur **8**:1, 1894.

3. Adami, Abbott and Nicholson: J. Exper. Med. **4**:349, 1899.

4. Kyes, P.: J. Infect. Dis. **18**:277, 1916.

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8. Louros, N., and Scheyer, H. E.: Ztschr. f. d. ges. exper. Med. **52**:291, 1926.

9. Bartlett, C. J., and Ozaki, Y.: J. M. Research **35**:465, 1916.

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12. Robertson, O. H.; Woo, S. T.; Cheer, S. N., and King, L. P.: J. Exper. Med. **47**:317, 1928.

13. Wright, H. D.: J. Path. & Bact. **30**:185, 1927.

nuclear and mononuclear leukocytes in the lungs and liver, and by the Küpffer cells of the liver coincident with the reduction of the number of organisms in the blood stream.

That clasmatoocytes play an important rôle in freeing the normal peritoneum from bacteria has been indicated by Jelin,<sup>14</sup> Jensen,<sup>15</sup> Noetzel,<sup>16</sup> Beattie,<sup>17</sup> Buxton and Torrey,<sup>18</sup> Bordet,<sup>19</sup> Wallgren<sup>20</sup> and Kanai<sup>21</sup> observed that the mononuclears played the most important part in the destruction of streptococcus in the blood stream and in the peritoneal cavity.

Gay and his collaborators have shown that there is a definite and constant correlation between accumulation of macrophages (clasmatoocytes) and resistance to streptococcus infection in the pleural cavity of rabbits (Gay and Morrison,<sup>22</sup> Gay and Clark,<sup>23</sup> Gay, Clark and Linton<sup>24</sup>). They observed that injection of various substances, such as aleuronat-starch and gum arabic-broth, into the pleural cavity in from eighteen to twenty-four hours produced an exudate predominantly polymorphonuclear and in seventy-two hours one predominantly mononuclear. When the cavity had been prepared seventy-two hours previously, animals were protected against many times the fatal dose of streptococcus "H" injected intrapleurally. The walls were thickened and filled with granulation tissue, and many of the cells were clasmatoocytes in which streptococci could be observed undergoing destruction. The animals were not protected against infection in a cavity prepared eighteen hours previously in which the pleural walls were filled almost exclusively with polymorphonuclear cells. The streptococci are phagocytosed both in the exudate and in the tissues almost exclusively by the mononuclear cells; phagocytosis by the polymorphonuclear cells is negligible. These studies show the remarkable protective value of the mobilization of macrophages against local streptococcus infections. Recently it has been shown that after collection of macrophages in one area they may be remobilized in other areas and afford some degree of protection (Gay, Clark and Linton,<sup>24</sup> Linton<sup>25</sup>).

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23. Gay, F. P., and Clark, A. R.: *J. Infect. Dis.* **36**:233, 1925.

24. Gay, F. P.; Clark, A. R., and Linton, R. W.: *Histologic Basis for Local Resistance and Immunity to Streptococcus*, *Arch. Path. & Lab. Med.* **1**:857 (June) 1926.

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Bass<sup>26</sup> injected streptococci into the pleural cavity of a normal and of an immunized rabbit and into a twenty-four hour broth prepared cavity, and noted that both polymorphonuclear and mononuclear cells were phagocytic. The phagocytosis was increased with immunization, and only then was the infection localized. He also injected streptococci into the bone-marrow of normal and immunized rabbits, and observed their phagocytosis almost entirely by the histiocytes.

The rôle of the accumulation of tissue macrophages (clasmatoocytes) in local infections with organisms other than streptococcus has been observed by a number of workers. Granulating wounds of rabbits were found resistant to staphylococcus and streptococcus but not to *Spirochaeta pallida* and *Pasteurella avicida* (Halley, Chesney and Dresel<sup>27</sup>). The accumulation of macrophages by intracutaneous injections of India ink afforded protection against the streptococcus but not against anthrax or diphtheria (Ledingham<sup>28</sup>). The injection of chemical irritants into the ears of rabbits protected them against the streptococcus but not against anthrax, diphtheria, or the pneumococcus (Cobbett and Melsome<sup>29</sup>). Nakahara<sup>30</sup> prepared the peritoneum of mice with olive oil and found that there occurred, coincident with the increase of macrophages, a local resistance to fatal doses of staphylococcus and pneumococcus as well as a quicker disposal of *B. coli*.

With a number of micro-organisms there appears to be no constant correlation between accumulation of macrophages and resistance to infections. There are conflicting reports in regard to protection against pneumococcus infections. Nakahara<sup>30</sup> obtained protection in the prepared peritoneum of mice. Singer and Adler<sup>31</sup> obtained protection against pneumococcus type III only in prepared pleural cavities of immunized rabbits. Tudoranu<sup>32</sup> obtained protection against pneumococcus III in prepared peritoneal cavities of rabbits only when immune serum was given. He observed phagocytosis by the exudate cells (mostly macrophages) only in the rabbits that had received immune serum. Recently it was found by Stuppy, Cannon and Falk<sup>33</sup> that after

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26. Bass, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **42**:269, 1925.

27. Halley, C. R. L.; Chesney, A. M., and Dresel, I.: Bull. Johns Hopkins Hosp. **41**:191, 1927.

28. Ledingham, J. C. G.: Brit. J. Exper. Path. **8**:12, 1927.

29. Cobbett, L., and Melsome, W. S.: Centralbl. f. allg. Pathol. u. path. Anat. **9**:827, 1898.

30. Nakahara, W.: J. Exper. Med. **42**:201, 1925.

31. Singer and Adler (footnote 11, first reference).

32. Tudoranu, G.: Ann. de l'inst. Pasteur **40**:606, 1926.

33. Stuppy, G. W.; Cannon, P. R., and Falk, I. S.: Proc. Soc. Exper. Biol. & Med. **36**:314, 1928.

vaccination in the upper respiratory tract of rabbits, the local immunity in the lungs was associated with an accumulation of histiocytes.

On account of these apparent irregularities in resistance to pneumococcus infections shown by these workers and in view of the fact that the studies of Gay and his collaborators have shown that the mobilization of macrophages plays an important rôle in enhanced resistance to streptococcus infections in the pleural cavities of rabbits, it was suggested that a similar study of pneumococcus infections would be of interest. The following series of experiments were undertaken to ascertain what effect accumulation of clasmatoocytes had on resistance to the pneumococcus.

#### INJECTION OF PNEUMOCOCCUS INTO PREPARED PLEURAL CAVITIES OF RABBITS

*Technic.*—A virulent strain<sup>34</sup> of pneumococcus type I was used for the infection of the pleural cavities of rabbits. Less than 0.0000001 cc. of an eighteen hour blood infusion-broth culture intrapleurally was a fatal dose. The virulence of successive cultures was tested from time to time by the intrapleural route. The pleural fluid of rabbits dying with pneumococcus pleurisy was removed and kept on ice. Rabbit blood infusion-broth cultures were made from the pleural fluid when needed and diluted in broth. A pleural fluid which had been kept for more than from three to four weeks was seldom used. Broth dilutions of from eighteen to twenty-four hour cultures were injected intrapleurally in 1 cc. amounts, and 1 cc. of several of the higher dilutions was plated out in rabbit blood, 0.2 per cent, dextrose infusion-agar and incubated forty-eight hours for the determination of the number of organisms injected.

The cells were mobilized in the pleural cavities of rabbits by injections of aleuronat-starch or gum arabic-broth. The resistance of the cavity was tested by the injection of the pneumococcus at either eighteen or seventy-two hour intervals after preparation.

*Injection of Pneumococcus into Seventy-Two Hour Prepared Pleural Cavity.*—EXPERIMENT 1.—Five cubic centimeters of 5 per cent aleuronat and 3 per cent starch in physiologic solution of sodium chloride was injected into the pleural cavities of four rabbits. One cubic centimeter of broth dilutions of an eighteen hour broth culture of a pleural fluid containing pneumococcus type I was injected into the prepared cavities of these rabbits (seventy-two hours later), with four rabbits used as controls. One cubic centimeter of the dilutions was plated out, and the colonies were counted. (The figures in table 1 and in the two succeeding tables are obtained from the average made from the number of colonies on these plates and represent the approximate number of pairs or chains injected.)

RESULTS.—All the rabbits died except one control and one prepared rabbit which had received the smallest dose (table 1). Apparently there was no protection afforded by this preparation. Animals were not protected against approximately five pairs or chains of pneumococci.

34. The strain was furnished by Julia T. Parker of the Department of Pathology, College of Physicians and Surgeons, Columbia University.

Three later experiments gave similar results. In one of these, however, slight protection was shown when the broth culture used was made from a pleural fluid which had been kept almost a month, thus possibly being less virulent. Three of the four prepared rabbits survived a small dose which was fatal to the controls. No protection was obtained in two experiments in which gum arabic-broth (instead of aleuronat-starch) was injected into the pleural cavity of the rabbits, which were infected seventy-two hours later with varying doses of eighteen hour broth culture of pneumococcus I.

From these experiments, when a seventy-two hour preparation was used, it can be said that little if any protection is afforded against pneumococcus infection. At the most, animals were protected only against from four to five fatal doses.

As the presence of pleural exudates, with a relatively high number of clasmatocytes and an accumulation of macrophages in thickened

TABLE 1.—*Effect of Seventy-Two Hour Preparation with Aleuronat-Starch on Resistance of Rabbits to Intrapleural Injection of Pneumococcus Type I*

Rabbits	Preparation	Amount of Culture Injected		Results
1561.....	Aleuronat-starch	0.000001	cc. = 50 colonies*	Dead, 26 hours
1574 (control)....	.....	0.000001	cc. = 50 colonies	Dead, 24 hours
5576.....	Aleuronat-starch	0.0000001	cc. = 5 colonies	Dead, 48 hours
1560.....	Aleuronat-starch	0.0000001	cc. = 5 colonies	Dead, 24 hours
5579 (control)....	.....	0.0000001	cc. = 5 colonies	Dead, 48 hours
1576 (control)....	.....	0.0000001	cc. = 5 colonies	Dead, 26 hours
5577.....	Aleuronat-starch	0.00000002	cc. = 1 colony	Survived
5574 (control)....	.....	0.00000002	cc. = 1 colony	Survived

\* The number of colonies represents the average number of pairs or chains of organisms injected.

pleural walls, failed to increase the resistance of the rabbits, the question arose whether the presence of a polymorphonuclear exudate and an inflamed pleura with many polymorphonuclears might not protect against pneumococcus. Workers have attributed much importance to the phagocytosis of pneumococcus by these cells. In vitro, the polymorphonuclear as well as the mononuclear cells of these pleural exudates were found to be slightly phagocytic for our strain. Consequently, in two experiments a twenty-four hour preparation of the cavity was used which gives an exudate in which polymorphonuclears predominate. The result of one of these is given in table 2.

*Injection of Pneumococcus into Twenty-Four Hour Prepared Pleural Cavity.*  
—EXPERIMENT 2.—Aleuronat and starch were injected into the pleural cavities of six rabbits. Twenty-four hours later, intrapleural injections of 1 cc. of broth dilutions of eighteen hour broth culture of pneumococcus were made into these rabbits and two used as controls.

RESULTS.—All of the rabbits died, even when a dose as small as 0.0000001 cc. of the culture was injected (table 2). Thus apparently no protection was afforded

rabbits against an intrapleural injection of pneumococcus type I when the cavity had been prepared only twenty-four hours previously with aleuronat-starch.

The prepared cavities were not resistant to injections of pneumococcus, neither those containing an exudate predominantly polymorphonuclear with an inflamed pleura nor those containing an exudate with many mononuclear cells and a thickened pleura containing granulation tissue and many macrophages.

The mobilization of clasmatoocytes which Gay and his collaborators found produced such a remarkable increase in the resistance of rabbits to intrapleural infections with streptococcus caused no appreciable increase in their resistance to this strain of pneumococcus. There was not much difference in the virulence of these two organisms when they were injected intrapleurally. Less than 0.0000001 cc. of broth cultures of either organism was fatal for rabbits; however, death occurred much more rapidly after an injection of pneumococcus than after one of streptococcus. With the pneumococcus there was rapid invasion of the blood stream from both prepared and normal cavities. This accumulation of cells did not localize the infection. Microscopic examination showed that there was much less phagocytosis of the pneumococcus than of the streptococcus when small

TABLE 2.—*Effect of Twenty-Four Hour Preparation with Aleuronat-Starch on Resistance of Rabbits to Intrapleural Injection of Pneumococcus Type I*

Rabbits	Preparation	Amount of Culture Injected	Results
4551.....	Aleuronat-starch	0.000001 cc. = 100 colonies*	Dead, 21 hours
4557.....	Aleuronat-starch	0.000001 cc. = 100 colonies	Dead, 24 hours
4554.....	Aleuronat-starch	0.0000005 cc. = 50 colonies	Dead, 24 hours
4556.....	Aleuronat-starch	0.0000005 cc. = 50 colonies	Dead, 24 hours
4553 (control)....	.....	0.0000002 cc. = 20 colonies	Dead, 24 hours
4551.....	Aleuronat-starch	0.0000001 cc. = 10 colonies	Dead, 24 hours
4500.....	Aleuronat-starch	0.0000001 cc. = 10 colonies	Dead, 3 days
4530 (control)....	.....	0.0000001 cc. = 10 colonies	Dead, 48 hours

\* The number of colonies represents the average number of pairs or chains of organisms injected.

amounts of broth cultures of these organisms were incubated with small amounts of exudates from either twenty-four or seventy-two hour prepared pleural cavities. Seldom did more than from 3 to 5 per cent of the clasmatoocytes phagocytose the pneumococcus, while 15 per cent of the clasmatoocytes of the same exudates phagocytosed the streptococcus. No pneumococci were found in the macrophages in the few examined walls of the seventy-two hour prepared cavities of rabbits killed shortly after the injection of a relatively large number of organisms.

This lack of protection in prepared cavities might be due to the resistance of our virulent strain of pneumococcus to phagocytosis. Many workers have noted that virulent cultures are not phagocytosed by leukocytes in vitro. Rosenow<sup>35</sup> showed that bacteria which fail to absorb opsonins show great resistance to phagocytosis. With physiologic solution of sodium chloride he was able to extract from virulent pneumococci a substance, "virulin," which inhibited the action of pneumococcus opsonin; after the extraction of the substance from pneumococci, they became phagocytosed. The extracts of virulent pneumococci or the

35. Rosenow, E. C.: J. Infect. Dis. 4:285, 1907.



filtrates of broth cultures of these organisms possess a soluble substance which reduces the phagocytosis of avirulent pneumococci and increases their virulence (Rosenow,<sup>35</sup> Felton and Bailey<sup>36</sup>).

*Injection of Washed Pneumococcus into Seventy-Two Hour Prepared Pleural Cavities.*—It was thought possible that these soluble specific substances, "virulins," "aggressins," might be responsible for the failure to get local intrapleural protection against this virulent strain of pneumococcus type I. With this in mind, several experiments were performed to determine whether rabbits offered more resistance to infection with washed organisms than with the unwashed organisms and might be protected against doses of washed pneumococcus by the mobilization of macrophages.

Pneumococci from an eighteen hour broth culture were washed twice in physiologic solution of sodium chloride. Some of the washed organisms were resuspended in broth and others in the Berkefeld filtrate from some of the culture. Corresponding broth dilutions of the suspensions were injected into rabbits having a seventy-two hour prepared cavity and into normal rabbits. In two experiments all of the prepared animals given injections with washed organisms, which had been in contact with the filtrate, as well as all of the control rabbits, died. Only those prepared rabbits survived (two out of three) which had received the smallest doses (from five to thirteen pairs or chains) of the washed organisms resuspended in broth. This showed a slight amount of protection.

The carrying out of well controlled experiments was difficult, as during the process of washing in physiologic solution of sodium chloride and diluting, many of the organisms were either destroyed or so injured that they were sensitive to changes in temperature and to the nature of the medium. Plating showed that some died in the broth in the interval between the making of the dilutions and the infection of the animals. When Locke's solution was used, instead of saline, the decrease in the number of organisms was not so great, and approximately the same number of organisms could be given in corresponding dilutions. Falk and Yang<sup>37</sup> avoided the use of saline for washing pneumococcus on account of a possible detrimental effect. It was found advisable not to subject the organisms to more thorough washing and to use Locke's solution instead of saline.

EXPERIMENT 3.—*A.* Centrifugated organisms from 2 cc. of an eighteen hour broth culture of pneumococcus type I were washed in Locke's solution and then in infusion broth. They were resuspended in broth, and broth dilutions were made. One cubic centimeter of varying dilutions was plated out, and 1 cc. of

36. Felton, L. D., and Bailey, G. H.: J. Infect. Dis. **38**:131, 1926.

37. Falk, I. S., and Yang, S. Y.: J. Infect. Dis. **38**:1, 1926.

these dilutions was injected into the cavities of three rabbits prepared with seventy-two hour aleuronat-starch and into three controls in series A, table 3.

B. Centrifugated organisms from 2 cc. of the eighteen hour broth culture, after being washed in Locke's solution, were washed in the Berkefeld filtrate of a portion of the culture, and resuspended in the filtrate. Broth dilutions were made and 1 cc. of the dilutions was plated and 1 cc. injected into pleural cavities of three prepared and three control rabbits in series B, table 3.

RESULTS.—All the control rabbits of both series died. All the prepared rabbits, receiving the washed organisms, which had been in contact with the filtrate, died. All the prepared rabbits that received the washed organisms, resuspended in broth, died, except the one that received the smallest dose (table 3).

The pneumococci, which had been subjected to several washings in physiologic solution of sodium chloride or in Locke's solution and broth, were still virulent

TABLE 3.—*Effect of Seventy-Two Hour Preparation with Aleuronat-Starch on Resistance of Rabbits to Intrapleural Injection of Washed Pneumococcus*

A. Pneumococci from broth culture washed in Locke's solution, in broth and resuspended in broth. Dilutions made in broth. Forty-seven colonies from 1 cc. of 1:1,000,000 dilution			
Rabbits	Preparation	Amount of Pneumococcus Suspension Injected	Results
1634.....	Aleuronat-starch	0.000001 cc. = 47 colonies	Dead, 28 hours
1641 (control)....	.....	0.000001 cc. = 47 colonies	Dead, 28 hours
1635.....	Aleuronat-starch	0.0000002 cc. = 10 colonies	Dead, 36 hours
1642 (control)....	.....	0.0000002 cc. = 10 colonies	Dead, 36 hours
1636.....	Aleuronat-starch	0.00000005 cc. = +2 colonies	Survived
1650 (control)....	.....	0.00000005 cc. = +2 colonies	Dead, 28 hours
B. Pneumococci from broth culture washed in Locke's solution, in Berkefeld filtrate of portion of culture, and resuspended in filtrate. Dilutions made in broth. Forty-nine colonies from 1 cc. of 1:1,000,000 dilution			
Rabbits	Preparation	Amount of Pneumococcus Suspension Injected	Results
1637.....	Aleuronat-starch	0.000001 cc. = 49 colonies	Dead, 36 hours
1649 (control)....	.....	0.000001 cc. = 49 colonies	Dead, 28 hours
1638.....	Aleuronat-starch	0.0000002 cc. = 10 colonies	Dead, 36 hours
1651 (control)....	.....	0.0000002 cc. = 10 colonies	Dead, 24 hours
1639.....	Aleuronat-starch	0.00000005 cc. = +2 colonies	Dead, 36 hours
1648 (control)....	.....	0.00000005 cc. = +2 colonies	Dead, 24 hours

for the rabbits. Animals with prepared cavities were only slightly more resistant to the washed organisms than to the unwashed pneumococci or to those that had been washed and subsequently brought into contact with the broth culture filtrate. There was no marked difference in the susceptibility of the washed and unwashed organisms to phagocytosis in vitro by cells of the exudates, except that with washed organisms the mononuclear cells seemed slightly more active.

These results appear to be in accord with the work of Miss Pittman, which is mentioned by Falk,<sup>38</sup> who considered the specific substances on the pneumococcus, their encapsulation and high potential difference and not the secreted soluble substances important. It would appear from our experiments, in which protection was so slight against the washed

38. Falk, I. S.: *Newer Knowledge of Bacteriology and Immunology*, Chicago, University of Chicago Press, 1928, p. 565.

organisms, that the soluble specific substance on the pneumococci was not the essential factor in preventing protection by mobilized clasmato-cytes in the pleural cavities and adjacent tissues.

As washing the pneumococci made them only slightly more susceptible to phagocytosis by the mononuclear cells of the exudates and the prepared cavity was only slightly more resistant to them, another means of increasing their susceptibility to phagocytosis by the macrophages was sought. It was decided to try antiserum.

#### ADDITION OF ANTISERUM TO PNEUMOCOCCUS BEFORE INJECTION INTO THE PLEURAL CAVITY

Denys and LeClef<sup>39</sup> noted that the recovery of immunized rabbits from streptococcus infection apparently was due to phagocytosis, made possible by the immune serum. Neufeld and Rimpau,<sup>40</sup> working with serums derived from animals immunized with streptococci and pneumococci, concluded that the serum contained "bacteriotropins" which altered the bacteria so as to make them susceptible to phagocytosis. Kanai<sup>21</sup> injected antiserum with streptococcus into the peritoneum of mice and observed that its protective value was associated with increased phagocytosis by the leukocytes, especially by the mononuclears. Bass,<sup>26</sup> studying bone marrow and intrapleural streptococcus infections in normal rabbits and those that had been immunized intravenously, found increased phagocytosis in the histiocytes and mononuclear cells as well as in the polymorphonuclear cells. Protection against intrapleural streptococcus infection was obtained with immunization and not with twenty-four hour preparation of the cavity alone. There was marked phagocytosis by the histiocytes when he injected sensitized streptococcus into the bone marrow. He concluded that the macrophages react to the opsonized organisms as do the leukocytes, and that immunity depends chiefly on the phagocytosis and digestion of the cocci by the reticulo-endothelial system (histiocytes, tissue macrophages or clasmatocytes).

When antiserum diluted with broth was added to our strain of pneumococci, they became susceptible to phagocytosis by the cells of the pleural exudates. After a short incubation, as many as 19 per cent of the polymorphonuclear cells and 34 per cent of the clasmatocytes contained pneumococci. Organisms which had been in contact with antiserum for a short time and had then been resuspended in broth were also susceptible to phagocytosis by the cells. When a sufficient amount of antiserum, e. g., 1 cc., together with our strain of pneumococcus, was injected intrapleurally into a normal rabbit the animal was protected.

39. Denys, J., and LeClef, J.: *Cellule* **11**:175, 1895.

40. Neufeld, F., and Rimpau, W.: *Deutsche med. Wchnschr.* **2**:1458, 1904.

On account of the increase in phagocytosis by the exudate cells of the sensitized pneumococci and the results obtained by Bass<sup>26</sup> with streptococci, it was thought that with the accumulation of clasmatocytes in a prepared pleural cavity, local protection might be obtained against an infection with pneumococci previously in contact with antiserum.

*Injection of Pneumococcus that Had Been in Contact with Antiserum in a Seventy-Two Hour Pleural Cavity.*—EXPERIMENT 4.—Two cubic centimeters of a broth culture of pneumococcus type I was centrifugated. To the centrifugated organisms was added 0.4 cc. of antipneumococcus serum.<sup>41</sup> After thirty minutes' incubation, 1.6 cc. of broth was added, the organisms were resuspended, and broth dilutions were made. Intrapleural injections of 1 cc. of corresponding dilutions were made into eight normal rabbits and eight rabbits in which the cavities had

TABLE 4.—*Effect of Seventy-Two Hour Preparation with Aleuronat-Starch on Intrapleural Injections of Pneumococcus Type I Which Had Been in Contact with Type I Antiserum*

Rabbits	Preparation	Amount of Suspension Injected		Results
1596.....	Aleuronat-starch	0.0001 cc.	= 900 colonies*	Dead, 48 hours
1609 (control)....	.....	0.0001 cc.	= 900 colonies	Dead, 24 hours
1597.....	Aleuronat-starch	0.00002 cc.	= 180 colonies	Dead, 48 hours
1598.....	Aleuronat-starch	0.00002 cc.	= 180 colonies	Dead, 72 hours
1610 (control)....	.....	0.00002 cc.	= 180 colonies	Dead, 48 hours
1611 (control)....	.....	0.00002 cc.	= 180 colonies	Dead, 48 hours
1599.....	Aleuronat-starch	0.00001 cc.	= 90 colonies	Survived
1600.....	Aleuronat-starch	0.00001 cc.	= 90 colonies	Survived
1612 (control)....	.....	0.00001 cc.	= 90 colonies	Dead, 24 hours
1613 (control)....	.....	0.00001 cc.	= 90 colonies	Dead, 48 hours
1601.....	Aleuronat-starch	0.000002 cc.	= 18 colonies	Survived
1602.....	Aleuronat-starch	0.000002 cc.	= 18 colonies	Survived
1614 (control)....	.....	0.000002 cc.	= 18 colonies	Dead, 24 hours
1615 (control)....	.....	0.000002 cc.	= 18 colonies	Dead, 24 hours
1603.....	Aleuronat-starch	0.000001 cc.	= 9 colonies	Survived
1616 (control)....	.....	0.000001 cc.	= 9 colonies	Dead, 48 hours

\* The number of colonies represents the average number of clumps of organisms (not pairs or chains) in 1 cc. of broth dilutions. The microscopic examination of broth dilution (1:100) showed organisms mostly in clumps, often containing thirty chains.

been prepared seventy-two hours previously. Broth dilutions were plated out, the colonies were counted and an average was made. The lower dilutions were examined microscopically.

RESULTS.—All the prepared rabbits receiving the three smaller doses of sensitized pneumococcus were protected (table 4). All the control rabbits receiving the same doses died. The prepared rabbits withstood 0.00001 cc. of the suspension of the pneumococci which had been in contact with antiserum, while 0.000001 cc. of the suspension was fatal to the animal used as control.

It was difficult to estimate with any accuracy the number of living organisms injected, as they had been agglutinated by the serum and there were many clumps. The animals were certainly given many more organisms than the figures show. In a preliminary experiment with pneumococci that had been in contact with antiserum, both control rabbit and prepared rabbit lived when 0.0000001 cc. of the

41. The serum used was horse serum, diagnostic pneumococcus type I antiserum from the Department of Health, New York.

suspension was given. When 1 cc. of that dilution was plated out, no colonies were seen, so it is impossible to say whether the unprepared rabbit had received even one clump of organisms. It can at least be said that prepared rabbits (table 4) receiving pneumococci that had been in contact with antiserum were protected against more than ten times the number that was fatal to unprepared animals. The same result had been found in two previous experiments. In a later experiment a rabbit was protected against more than 100 times the fatal dose for an unprepared animal.

These experiments showed that a local protection against pneumococcus I was attained in seventy-two hour prepared pleural cavities containing mononuclear exudates, with thickened pleuras containing many macrophages when the organism had been in contact with a specific immune serum. The protection afforded was almost as marked as that found by Gay and his collaborators against unsensitized streptococcus. These results are somewhat similar to those obtained by Tudoranu,<sup>22</sup> working with type III. He obtained protection in twenty-four hour broth-prepared peritoneums when he injected immune serum previously and simultaneously with the organisms, but not when he injected normal serum. He noted that phagocytosis was negligible unless immune serum had been injected. He considered that the antibodies, neutralizing the aggressins, permitted the production of an exudate, rich in leukocytes, which changes the pneumococci and renders them susceptible to phagocytosis.

Gay and his collaborators, in their local passive immunity experiments (Gay and Morrison,<sup>22</sup> Gay and Clark<sup>23</sup>), found a more rapid disappearance of streptococci from the pleural cavity when rabbit immune serum was given both previously and simultaneously with the injection than when normal serum was used. Streptococci showed greater susceptibility to phagocytosis by the exudate cells with immune serum than with normal serum. In the experiments with pneumococci the effect of the addition of normal rabbit or horse serum was not tried, but it is indicated by the result obtained in a later experiment designed to give some suggestions regarding the mechanism of this protection. It appears that in order to get local protection against this virulent strain of pneumococcus type I by the seventy-two hour preparation of the cavity, the organisms must first be altered by contact with immune serum and become susceptible to phagocytosis.

If the addition of a serum with its specific immune properties (demonstrable antibodies such as agglutinins and bacteriotropins) to the pneumococcus was necessary in order to obtain protection in prepared pleural cavities of rabbits, the reduction of the antibodies in the serum should lessen the protective value of the serum and thus decrease the resistance afforded by the accumulation of the macrophages.

Gay and Chickering,<sup>42</sup> with the addition of an extract of pneumococcus to homologous antiserum, produced a precipitate which carried down the antibodies that protect animals against pneumococcus infection. Felton and Bailey<sup>43</sup> extracted a specific substance from pneumococcus type II, which was nontoxic for mice but gave an antagonistic effect on the defense of these animals or increased the virulence of the organisms. They observed that it neutralized the protective effect of the pneumococcus serum in vivo and in vitro. With this soluble specific substance all protective substances could be precipitated. The agglutinative, precipitative and tropinizing activities were absorbed out of the serum by the filtrate. Wadsworth and Sickles<sup>44</sup> found that the supernatant fluid or filtrate of broth culture of a virulent strain of type I had an inhibitory effect on phagocytosis of virulent strains in the presence of specific antiserum, and that this action was on the serum rather than on the leukocytes.

The effect of the addition of a filtrate from a fourteen day broth culture of our strain of pneumococcus to the antiserum was observed in vitro. When the Berkefeld filtrate of a fourteen day broth culture of this strain was added to some of the antiserum a precipitate was formed. Centrifugated organisms from an eighteen hour culture when resuspended in the resulting supernatant fluid were not so completely agglutinated nor so readily phagocytosed by the exudate cells as the organisms that had been resuspended in the antiserum in broth. When small amounts of these two suspensions were incubated with a pleural exudate, those in the antiserum in broth were found in 19 per cent of the polymorphonuclear and 34 per cent of the mononuclear cells, whereas those suspended in the supernatant fluid were phagocytosed only by 7 per cent of the polymorphonuclear and 16 per cent of the mononuclear cells.

The addition, then, of a Berkefeld filtrate of the fourteen day broth culture to the antiserum removed some of its agglutinative and tropinizing activities.

Rabbits were given intrapleural injections of pneumococci which had been in contact with the resulting supernatant fluid in order to determine whether protection could be obtained.

*Injection of Pneumococci Which Had Been in Contact with Antiserum After the Addition of Filtrate of a Broth Culture.*—EXPERIMENT 5.—A. Infusion broth, 1.6 cc., was added to 0.4 cc. of antiserum and this mixture was added to the centrifugated organisms from 2 cc. of an eighteen hour broth culture of pneumo-

42. Gay, F. P., and Chickering, H. T.: J. Exper. Med. **21**:389, 1915.

43. Felton, L. D., and Bailey, G. H.: J. Infect. Dis. **38**:145, 1926; (foot-note 36).

44. Wadsworth, A. B., and Sickles, G. M.: J. Immunol. **14**:321, 1927. Sickles, G. M.: Ibid. **14**:329, 1927.

coccus. After thirty minutes broth dilutions of the suspension were made, and 1 cc. of dilutions was plated out; intrapleural injections of 1 cc. were made into rabbits in series A, table 5. Four rabbits had received aleuronat-starch intrapleurally seventy-two hours previously, and three normal rabbits were used as controls.

B. Two cubic centimeters of a Berkefeld filtrate of a fourteen day culture of the pneumococcus was added to 0.5 cc. of antiserum. This mixture was centrifugated after standing one hour, and 2 cc. of the supernatant fluid was added to the centrifugated organisms from 2 cc. of the eighteen hour broth culture of pneumococcus. Half an hour later, dilutions of this suspension were made in broth. Broth dilutions were plated out in 1 cc. amounts and injections of 1 cc. were made into the pleural cavities of the rabbits in series B, table 5. Four

TABLE 5.—*Effect of the Addition of Broth Culture Filtrate to Antiserum on Resistance of Rabbits to Intrapleural Injections of Pneumococcus, After Seventy-Two Hour Preparation with Aleuronat-Starch\**

A. Injection of broth dilutions of suspension of pneumococcus which had been in a mixture of antiserum and broth			
Rabbits	Preparation	Amount of Suspension Injected	Results
1623.....	Aleuronat-starch	0.00002 cc. = 1,600 colonies	Survived
1624.....	Aleuronat-starch	0.00001 cc. = 800 colonies	Survived
1625.....	Aleuronat-starch	0.000002 cc. = 160 colonies	Survived
1632 (control)....	.....	0.000002 cc. = 160 colonies	Dead, 72 hours
1630.....	Aleuronat-starch	0.000001 cc. = 80 colonies	Survived
1645 (control)....	.....	0.000001 cc. = 80 colonies	Dead, 21 hours
1640 (control)....	.....	0.0000002 cc. = 16 colonies	Dead, 48 hours
B. Injection of broth dilutions of suspension of pneumococcus which had been in supernatant fluid from the mixture of antiserum and Berkefeld filtrate of fourteen day broth culture			
Rabbits	Preparation	Amount of Suspension Injected	Results
1626.....	Aleuronat-starch	0.00001 cc. = 2,000 colonies	Dead, 21 hours
1627.....	Aleuronat-starch	0.000002 cc. = 400 colonies	Dead, 21 hours
1633 (control)....	.....	0.000002 cc. = 400 colonies	Dead, 48 hours
1631.....	Aleuronat-starch	0.000001 cc. = 200 colonies	Dead, 26 hours
1643 (control)....	.....	0.000001 cc. = 200 colonies	Dead, 21 hours
1622.....	Aleuronat-starch	0.0000002 cc. = 40 colonies	Dead, 21 hours
1644 (control)....	.....	0.0000002 cc. = 40 colonies	Dead, 21 hours

\* The number of colonies represents the clumps of organisms, not the pairs or chains. Microscopic examination of the broth dilution (1:10) of organisms used in series A showed organisms mostly in clumps with an average of thirty-four chains; 1:10 dilution of those used in B showed fewer and smaller clumps, with an average of eight chains.

rabbits had received intrapleural injections of aleuronat-starch seventy-two hours previously, and three normal rabbits were used as controls.

RESULTS.—All of the prepared rabbits survived in series A (table 5); all of the control rabbits died. All the animals, both prepared and controls, died in series B (table 5).

All the prepared animals were protected against the organisms that had been in contact with antiserum and broth. A rabbit was protected against approximately 1,600 clumps of pneumococci, which was 100 times the number that was fatal to a control rabbit (rabbits 1623, 1640, table 5). None of the rabbits was protected against the pneumococci that had been in the supernatant fluid from the antiserum and culture filtrate; a prepared rabbit did not withstand a dose containing approximately forty clumps of these pneumococci (rabbit 1622, table 5).

This experiment shows that by the addition of culture filtrate to the antiserum, which decreases its agglutinating and tropinizing effect, there had been a decrease in the protective value. It indicates that contact of the pneumococcus with a

serum containing these properties is necessary before protection can be obtained in a rabbit by a preparation that causes an accumulation of macrophages.

The failure to obtain protection against our strain of pneumococci by a seventy-two hour preparation, which causes an accumulation of macrophages in the pleural cavity and affords a marked protection against sensitized pneumococci, would appear to be due to an insufficient amount of agglutinative and tropinizing activity in the rabbit.

Robertson and Sia<sup>45</sup> found that the serum of resistant animals, dogs and cats, possessed pneumococcidal properties, but that that of susceptible animals, as rabbits, did not. Virulent pneumococci, after contact with serum of resistant animals, were phagocytosed by the leukocytes from susceptible as well as from resistant animals, but this was not the case after contact with serum of susceptible animals. They considered opsonins important in resistance to pneumococcus infections. Bull<sup>46</sup> considered agglutinins, as well as opsonins, important.

*Injection of Pneumococci That Had Been in Contact with Antiserum into an Eighteen Hour Prepared Cavity.*—As the seventy-two hour preparation of the pleural cavity afforded protection against pneumococcus that had been in contact with antiserum, the question arose as to whether it was necessary to have an accumulation of macrophages for protection or whether an accumulation of polymorphonuclear cells would protect the rabbits against these organisms. The polymorphonuclear cells of the pleural exudate in vitro had appeared also phagocytic for the pneumococcus that had been in contact with the antiserum. In eighteen hours an injection of aleuronat-starch produces an exudate rich in polymorphonuclear cells. Table 6 gives the results of the infection of an eighteen hour prepared cavity with pneumococci that had been in contact with antiserum.

EXPERIMENT 6.—Two cubic centimeters of a twenty hour broth culture of the pneumococcus was centrifugated. To these organisms 0.4 cc. of antiserum was added. After thirty minutes, 1.6 cc. of broth was added, and the suspension was diluted in broth. Intrapleural injections of 1 cc. of some of the broth dilutions were made into two normal rabbits and three rabbits that had received injections of aleuronat-starch eighteen hours previously.

RESULTS.—As table 6 shows, no protection was apparent. A prepared rabbit receiving only 0.000001 cc. of the suspension (eight clumps) was not protected (rabbit 1579, table 6).

The same results were shown in a later experiment. An inflamed pleural cavity containing an exudate predominantly polymorphonuclear does not protect rabbits against the injection of pneumococci that have been in contact with antiserum.

45. Robertson, O. H., and Sia, R. H.: J. Exper. Med. **39**:219, 1924; *ibid.* **46**:237, 1927.

46. Bull, C. G.: J. Exper. Med. **22**:457, 1915; *ibid.* **24**:7, 1916.



As the rabbits with seventy-two hour prepared cavities are protected against more than 100 times the number of treated pneumococci which are still fatal for unprepared rabbits or for those with eighteen hour prepared cavities, it would appear that the protection is essentially due to the accumulation of clasmotocytes.

A few studies were made of the action of a seventy-two hour pleural exudate on the pneumococcus in vitro and in vivo to determine whether the exudate played an important part in the protection.

*The Injection of Seventy-Two Hour Pleural Exudate and Pneumococci that Had Been in Contact with Antiserum into the Normal Pleural Cavity.*—EXPERIMENT 7.—The centrifugated organisms from 2 cc. of a twenty hour broth culture

TABLE 6.—*Effect of Eighteen Hour Preparation with Aleuronat-Starch on Intrapleural Injections of Pneumococcus Type 1 Which Had Been in Contact with Antiserum*

Rabbits	Preparation	Amount of Suspension Injected	Results
1570.....	Aleuronat-starch	0.00001 cc. = 80 colonies*	Dead, 48 hours
1579.....	Aleuronat-starch	0.000001 cc. = 8 colonies	Dead, 28 hours
1572 (control)....	.....	.....	Dead, 25 hours
1568.....	Aleuronat-starch	0.0000001 cc. = ?	Lived
1572 (control)....	.....	.....	Lived

\* The number of colonies represents the average number of clumps of organisms in 1 cc. of broth dilutions of suspension of sensitized pneumococcus injected.

TABLE 7.—*Effect of Intrapleural Simultaneous Injection of Seventy-Two Hour Gum Arabic-Broth Pleural Exudate with Pneumococcus Which Had Been in Contact with Antiserum*

Rabbits	Injection	Amount of Suspension Injected	Results
1619.....	2 cc. exudate	+0.00001 cc. = 90 colonies*	Dead, 50 hours
1621 (control)....	Broth	+0.00001 cc. = 90 colonies	Dead, 35 hours
1622.....	2 cc. exudate	+0.000001 cc. = 9 colonies	Dead, 36 hours
1628 (control)....	Broth	+0.000001 cc. = 9 colonies	Survived

\* The number of colonies represents the average number of clumps of organisms in 0.5 cc. of dilutions of suspension of pneumococcus injected.

of pneumococcus were in contact with antiserum for twenty minutes. They were resuspended in broth, and broth dilutions were made. Then 0.5 cc. of the dilutions was added to 2 cc. of seventy-two hour pleural exudate and injected intrapleurally into normal unprepared rabbits. Injections of 0.5 cc. of corresponding dilutions of the organisms without the exudate were made into two other rabbits.

RESULTS.—Both rabbits receiving the exudate and the organisms died. The exudate did not protect a rabbit against an intrapleural dose not fatal to one that had received no exudate (table 7, 1620, 1628).

The transfer of a seventy-two hour pleural exudate to the normal pleural cavity does not protect rabbits against the pneumococci that had been in contact with antiserum. This experiment would suggest that the exudate does not have a bactericidal effect in vivo on the pneumococcus, nor does it play an important rôle in the local protection obtained against the pneumococcus by the seventy-two hour preparation of the pleural cavities of the rabbits.

In spite of the fact that the exudate did not confer protection on normal cavities against pneumococci that had been in contact with immune serum, it was thought there might be some bactericidal or inhibitory action by the exudate.

#### ACTION IN VITRO OF PLEURAL EXUDATE ON PNEUMOCOCCUS

In several experiments the pleural exudates had shown no bactericidal effect in vitro on our virulent strain of pneumococcus. The supernatant fluid from the exudate showed no bactericidal effect on these organisms, and they were not susceptible to phagocytosis by the cells. The contact with antiserum rendered them more susceptible to phagocytosis. Woo <sup>47</sup> found that a rabbit serum-leukocyte mixture had the power to kill avirulent pneumococcus but did not inhibit the growth of virulent organisms.

Tests were made to determine whether the exudate might have a bactericidal effect on the organisms that were washed or had been washed and in contact with antiserum.

TABLE 8.—*Bactericidal Effect of Exudate on Organisms*

	Results, 24 Hours
1. Exudate 1 cc. + 0.1 cc. pneumococcus ( $\pm 150$ ) .....	Growth
2. Exudate 1 cc. + 0.1 cc. pneumococcus which had been washed in Locke's solution and broth ( $\pm 47$ ) .....	Growth
3. Exudate 1 cc. + 0.1 cc. pneumococcus which had been washed in Locke's solution and broth and in contact with antiserum ( $\pm 34$ ).....	Growth

*Bactericidal Effect of Exudate in Vitro.*—EXPERIMENT 8.—Portions of a broth culture of pneumococcus were centrifugated and washed in Locke's solution. The sediment in one tube was washed in broth and resuspended in broth; the sediment in the second tube was placed in contact with antiserum and then resuspended in broth. Broth dilutions were made of the broth culture and of these suspensions. One-tenth of a cubic centimeter of dilution 1:100,000 of each of these was added to 1 cc. amounts of a seventy-two hour pleural exudate. (These were incubated at 37 C., and tested for sterility on blood-agar plates twenty-four hours later.) The number of chains or clumps of pneumococcus are indicated by the figures in table 8.

RESULT.—Growth was evident in the subcultures made from all of the tubes after twenty-four hours. In twenty-four hours the exudate had not been able to kill the small number of washed pneumococci and those that had been in contact with antiserum. The exudate showed no apparent bactericidal action on the pneumococcus.

In other experiments growth was obtained in the subcultures when as few as eight clumps of organisms that had been in contact with antiserum were added to the exudate and incubated for eighteen hours. On the other hand, Robertson and Sia <sup>48</sup> were not able to recover pneumo-

47. Woo, S. T.: J. Exper. Med. 43:623, 1926.

48. Robertson, O. H., and Sia, R. H.: J. Exper. Med. 40:467, 1924.

coccus after immune serum was added to a rabbit serum-leukocyte mixture. They used a mechanical agitator, and a larger amount of immune serum was present in their mixture than was still present in the broth dilution used by my co-workers and myself.

It was thought that microscopic examination might show slight evidence of growth inhibition as well as of marked phagocytosis by the exudate of the pneumococci to which antiserum had been added. Observations were made of the action in vitro of seventy-two hour

TABLE 9.—*Microscopic Observation of Phagocytosis and Growth of Pneumococcus in Seventy-Two Hour Pleural Exudate in Vitro*

Tube 1: Exudate plus Broth Dilution of Pneumococci Which Had Been in Contact with Antiserum and Broth			
Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½.....	8	10	4 (mostly clumps)
1.....	5	13	2 (mostly clumps)
2.....	2	7	5 (mostly clumps)
Tube 2: Exudate plus Broth Dilution of Pneumococci Which Had Been in Contact with Supernatant Fluid of Mixture of Antiserum and Filtrate			
Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½.....	1	5	70 (some small clumps)
1.....	2	7	86 (some small clumps)
2.....	0	5	300 (pairs and chains)
Tube 3: Exudate plus Broth Dilution of Pneumococci Which Had Been Resuspended in Broth			
Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½.....	0	2	98 (pairs and chains)
1.....	2	0	160 (pairs and chains)
2.....	0	0	300 (pairs and chains)
Tube 4: Exudate plus Broth Dilution of Pneumococcus Broth Culture			
Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½.....	0	2	45 (pairs and chains)
1.....	0	0	100 (pairs and chains)
2.....	0	0	140 (pairs and chains)

pleural exudates on organisms that had been in contact with antiserum. At the same time the observations included the effect of the addition of fourteen day broth culture filtrate to the antiserum. Broth dilutions of the culture and the broth suspension of the centrifugated organisms from some of the culture were used as controls.

EXPERIMENT 9.—To the centrifugated pneumococcus from 2 cc. of broth culture 0.4 cc. of antiserum plus 1.6 cc. of broth were added and incubated for twenty minutes. The supernatant fluid from a mixture of 0.4 cc. of antiserum and 1.6 cc. of filtrate of fourteen day broth culture was added to the centrifugated organisms from 2 cc. of the culture and incubated for twenty minutes. The centrifugated organisms from 2 cc. of the culture were resuspended in broth. Dilutions were

made in broth of suspensions and of the broth culture. One tenth of a cubic centimeter of the 1:10 dilutions was added to 0.1 cc. of seventy-two hour gum arabic pleural exudate and incubated for two hours. Stained smears were examined at different intervals.

RESULTS.—The pneumococci that had been in contact with antiserum were phagocytosed by the cells of the pleural exudate. The organisms did not appear to have multiplied within two hours. Those that had been in contact with the antiserum to which the filtrate had been added were not so susceptible to phagocytosis, and they had multiplied during the two hours. Very few of the untreated organisms from the culture were phagocytosed, and they were able to multiply in the exudate. Those organisms that had been in contact with antiserum showed

TABLE 10.—Study of Pleural Exudates from a Series of Rabbits Prepared by Injection of Aleuronat-Starch Followed from Sixty-Eight to Seventy-Two Hours Later by Injection of Relatively Large Dose of Pneumococcus Type I; 1 Cc. of Culture or Suspensions Injected

A. Injection of 1 Cc. of Suspension of Pneumococcus Which Had Been in Contact with Antiserum and Broth											
Rabbit	Dose*	Interval After Injection	Amount of Fluid, Cc.	Number of Cells in Millions per Cc.		Ratio of Bacteria Recovered to Those Injected	Percentage of Phagocytic Cells		Extracellular Bacteria, 100 Cells Counted	Presence of Pneumococcus in Blood	Presence of Pneumococcus in Left Cavity
				Polymorphonuclears	Mononuclears		Polymorphonuclears	Mononuclears			
1435	2,000,000	45 min.	6.5	47	8	0†	1	7	2	0	0
4598	10,000,000	1 hr.	5	?	?	×0.0001	—	—	0	0	0
693	5,000,000	2½ hr.	3	94	30	×0.0006	0	3	1	0	0
										(200 cells counted)	
B. Injection of 1 Cc. of Broth Suspension of Centrifugalized Pneumococcus from Broth Culture											
1534	9,000,000	45 min.	2.5	66	9	× 3	0.2	4	92	+	+
4597	45,000,000	1 hr.	6	?	?	× 0.26	1	1	38	+	0
690‡	260,000,000	2½ hr.	7	121	34	× 4.3	0.5	0	410	+	+

\* Figures under dose in series A represent the number of clumps; in series B, the number of pairs or chains of pneumococci.

† No colonies were seen when 0.5 cc. of exudate was plated out.

‡ 1 cc. of broth culture in 690.

susceptibility to phagocytosis by the exudate cells and to an inhibiting action of the exudate.

*Fate of Pneumococcus in the Seventy-Two Hour Prepared Pleural Cavity.*—A study was made of the fate of pneumococcus injected into the pleural cavities of a few rabbits prepared seventy-two hours previously with aleuronat-starch in order to obtain information that would explain still further the mechanism of the protection.

Injections of 1 cc. of broth cultures of the pneumococcus or broth suspensions of centrifugated organisms from broth cultures and organisms that had been in contact with antiserum and resuspended in broth were made. The animals were killed at different intervals. The exudates were removed and portions plated out to determine the presence and number of viable organisms. The exudates were examined microscopically for phagocytosed and extracellular bacteria. Cultures.

were made from the other pleural cavity and from the heart's blood. Table 10 gives the results of the observations.

RESULTS.—Very few organisms were recovered from the pleural exudates of the rabbits into which injections of organisms that had been in contact with anti-serum were made. There was a marked decrease in the number of viable organisms shown in the time intervals up to two and one-half hours. Microscopically, it was difficult to observe organisms in the exudate from these rabbits. On the other hand, with one exception there had been an increase in the number of organisms in the pleural cavities of the rabbits given injections with the organisms that had not been in contact with antiserum. There was only a small amount of phagocytosis. These organisms were found in the heart's blood in as short a time as forty-five minutes after injection; in two animals they were recovered from the uninoculated pleural cavity, whereas in the rabbits into which injections of sensitized pneumococci were made no organisms were recovered within two and one-half hours from the heart's blood or from the other pleural cavity.

The virulent pneumococci, not altered by immune serum so that they were not clumped or susceptible to phagocytosis, were capable of multiplying in the exudate in the prepared pleural cavity and rapidly invading the blood stream. These observations made for the few time intervals up to two and one-half hours suggest that the growth of the sensitized pneumococcus had been retarded and the spread of the organisms checked in a pleural cavity with an exudate containing many mononuclear as well as polymorphonuclear cells and a thickened pleura containing granulation tissue and many macrophages.

The rapid disappearance of these sensitized organisms from the exudate may be due to their phagocytosis by the mobilized cells in the thickened pleura of these seventy-two hour prepared pleural cavities. The thickened pleura containing many cells may prevent clumped or phagocytosed organisms from entering the blood stream.

To increase the resistance of rabbits and obtain local protection in the pleural cavity against virulent pneumococcus several factors are involved. In addition to a prepared cavity, with the accumulation of clasmatocytes and a thickened wall, the contact of the organisms with immune serum is necessary. The pneumococci then become clumped and susceptible to phagocytosis by the polymorphonuclear and mononuclear cells of the exudate, and their growth is retarded. These organisms—many clumped, others within the polymorphonuclear and mononuclear cells and a few free pairs or chains susceptible to phagocytosis by the clasmatocytes—may be confined in the pleural cavity by the thickened wall with its granulation tissue and many macrophages, and the rabbit may be protected.

In immunized rabbits, Singer and Adler obtained protection in prepared and unprepared cavities against pneumococcus type III. They attributed the protection to a change in the reticulo-endothelial cells and not to the circulating antibodies. Tudoranu emphasized the importance of antibodies in the protection against pneumococcus type III in prepared cavities of passively immunized rabbits. He considered that the antibodies neutralizing the aggressins accelerate the production of the exudate active against the pneumococci.

In our work we have gone a step further than these observers, since we prove conclusively that the accumulation of clasmatoocytes, and in addition the action of tropinizing antiserum is necessary to protect a sensitive area of the rabbit against a virulent pneumococcus.

#### SUMMARY AND CONCLUSIONS

This paper attempts to show what effect the accumulation of polymorphonuclears or of mononuclears in local areas may have on protection against pneumococcus infections.

The strain of pneumococcus type I used was found virulent for rabbits, producing an extensive pleurisy and a rapid invasion of the blood stream. This strain of pneumococcus washed in saline or sensitized by contact with antiserum was still virulent.

Mobilization of the cells was effected by the injection of aleuronat-starch. An eighteen hour preparation of the pleural cavity produces an exudate predominantly polymorphonuclear in character and an inflamed wall filled with polymorphonuclear cells. A seventy-two hour preparation produces an exudate predominantly mononuclear and a thickened wall filled with granulation tissue and many macrophages.

No protection was afforded rabbits against an intrapleural infection with pneumococcus type I by an eighteen hour previous preparation of the pleural cavity.

Slight, if any, protection was afforded rabbits against an intrapleural infection with pneumococcus type I, washed or unwashed, by a seventy-two hour preparation.

Neither normal nor eighteen hour prepared cavities, with polymorphonuclear exudates and an inflamed pleural wall, afforded protection against pneumococci that had been in contact with small amounts of antiserum.

A seventy-two hour preparation afforded a marked protection against pneumococci that had been in contact with the same amount of immune serum. A pleural cavity with an exudate rich in mononuclear cells and a thickened wall with granulation tissue and many macrophages protected the rabbit against a dose of sensitized pneumococci which was from ten to 100 times that which was fatal for normal rabbits or rabbits with acutely inflamed cavities.

From this study it appears that there is a definite correlation between accumulation of clasmatoocytes and resistance to pneumococcus infection in the pleural cavity of the rabbit. To obtain complete protection in rabbits against local infections with pneumococcus type I, however, the addition of serum antibodies is necessary.

# Laboratory Methods and Technical Notes

## ESTIMATION OF HEMOGLOBIN BY CELL CONCENTRATION

### Suggestions for Reclassification of the Anemias\*

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The present methods of estimating the hemoglobin content colorimetrically are subject to certain errors. Aside from technical difficulties, for example, those of the comparison of colors, the chief source of error appears to be the differences in the relative concentration of the erythrocytes. This may be easily shown in any one case by the determination of the cell-plasma ratio<sup>1</sup> at various times during the day. The proportion of cells to plasma undergoes physiologic variation owing chiefly to the inhibition of fluids, and to exercise and sweating.

With this in mind, I found that under ideal conditions governing the particular technical procedure estimations of the hemoglobin content in the same case not infrequently varied 10 per cent on the same day. This was always due to a change in the relative dilution of the erythrocytes by blood plasma. In order to determine the extent of this variation, the hemoglobin content of several hundred patients was studied both by the old and by the new methods. The latter consisted, in principle, of a complete centrifugation of the cellular elements and determination of the hemoglobin content undiluted by plasma.

#### METHOD

1. Shake a few grains of dry, powdered sodium citrate into a clean, dry capillary glass tube having an inside diameter of 4 mm. and a length of 10 cm.<sup>2</sup>
2. Holding the tube in the horizontal position or with the distal end slightly depressed, apply the proximal end to a bleeding puncture wound. A rapid, deep, incised wound of the finger made with a sharp lancet-headed needle will fill at least three such tubes with little or no pressure on the finger.
3. Fill the tube about two-thirds full and mix the blood with the citrate by alternately elevating and depressing one end.
4. Allow the blood to gravitate to one end, seal that end with a plug of paraffin and place a broad rubber band snugly around the length of the tube, thus sealing both ends. It is well to file the cut edges to avoid injury to the fingers or tearing of the rubber band.
5. Centrifugate at high speed (plugged end down) for a sufficient length of time to secure the maximal separation of cells and plasma. This is determined as the period of time after which repeated centrifugation no longer diminishes the

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\* Submitted for publication, April 26, 1929.

\* From the Laboratory of St. Bartholomew's Hospital.

1. Felsen, J.: The Cell-Plasma Ratio, Arch. Path. 8:269 (Aug.) 1929.

2. Felsen, J.: A Simple Method of Testing for Blood Compatibility, Arch. Path. 4:552 (Oct.) 1927.

length of the cell column. Once established, the same button on the rheostat and the same period of time may be used with every specimen.

6. File-mark the capillary tube (*a*) at the junction of the paraffin plug with the cell column and (*b*) at the junction of the cell column with the plasma column. Break off at both points, thus isolating the cells.

7. By means of a Sahli pipet, graduated at 10 and 20 mm., the tip of which is applied directly to either of the open ends of the cell column, draw up the cells to the mark "10" (10 c.mm.). Add this to the graduated Sahli tube containing tenth normal hydrochloric acid to the mark 10. Wash the pipet thoroughly by sucking up and expelling some of the same fluid. Shake the mixture well and then allow it to stand at least one minute or until the maximal change of color has been effected. Dilute with water to match the standard. When the Dare instrument is used, aspirate the cells from the capillary tube by means of a Sahli pipet, as before, to the mark "10." Then continue aspirating physiologic sodium

*A Comparison of the Old and the New Methods of Estimating the Percentage of Hemoglobin in the Blood*

Patient	Hemoglobin, per Cent		Red Cell Count	Cell-Plasma Ratio
	Old Method	New Method		
1.....	55	60	.....	0.66
2.....	80	75	4,670,000	0.50
3.....	95	90	5,010,000	0.90
4.....	85	95	4,390,000	0.63
5.....	80	82	4,170,000	0.72
6.....	90	74	4,480,000	....
7.....	98	80	5,250,000	....
8.....	90	90	4,680,000	0.66
9.....	84	75	5,120,000	0.80
10.....	90	80	4,860,000	0.60
11.....	75	85	4,280,000	0.56
12.....	55	60	.....	0.66
13.....	60	65	.....	1.10
14.....	70	75	3,580,000	0.28
15.....	75	70	4,280,000	0.56
16.....	90	94	4,480,000	0.75
17.....	110	80	7,040,000	1.50
18.....	50	65	3,000,000	0.22
19.....	70	70	3,340,000	0.50
20.....	80	82	.....	0.72

chloride solution to the mark "20." Eject the resulting mixture (10 c.mm. of cells and 10 c.mm. of saline solution) on to a hanging drop slide or a small watch glass. Mix thoroughly by alternately aspirating and expelling the mixture from the pipet, four or five times. Having secured a uniform mixture, take it up in the Sahli pipet and fill the Dare automatic pipet; the 20 c.mm. of fluid will completely fill the latter. Compare in the colorimeter.

This method of estimating hemoglobin on the basis of the concentration of the capillary cells has been in use in this laboratory for three years and has given uniformly accurate results in conjunction with the Sahli standard. It appears to possess a distinct advantage in that the estimations are made directly on undiluted cells. The factor of plasma dilution, which is well beyond the control of the examiner, is eliminated, regardless of the time of day.

The table records cases chosen from a series of several hundred in which the hemoglobin was estimated on the Sahli and Dare instruments by the old method and by the method based on concentration of the cells. The Sahli figures alone are given. In a comparison of similar



figures in the records of routine examinations made over a period of three years, the following conclusions were reached:

When the cell-plasma ratio  $\frac{c}{p}$  approximates 1 (i.e., when the cell column and the plasma column are approximately equal), the estimation of the percentage of hemoglobin by the cell concentration method yields a value most nearly approaching that obtained by the old method.

When the cell-plasma ratio is low (i.e., when the plasma content of the blood is relatively high), the new method gives a considerably higher percentage of hemoglobin than the old (patient 18). This is least marked when the red cells are impoverished in hemoglobin while the red cell count is high (patients 14 and 19).

In primary anemias, the cell-plasma ratio being low, the percentage of hemoglobin is found to be much higher than with the old method.

In chlorosis, the cell-plasma ratio being high, the percentage of hemoglobin is found to be the same or lower than with the old method, by reason of the low hemoglobin content of individual cells.

In polycythemia vera, the cell-plasma ratio being high, the percentage of hemoglobin is found to be lower than with the old method.

In secondary anemias associated with acute hemorrhage, the cell-plasma ratio being low, the percentage of hemoglobin is found to be either normal or low. This is due to the fact that cells are lost, rather than hemoglobin, the percentage of the latter being frequently normal as estimated by the concentration method. The difference between the old method and the new is due to the fact that the latter eliminates one variable factor—the diluent plasma. The importance of this observation is evident in repeated examinations of a patient with bleeding gastric or duodenal ulcer. Watching the cell-plasma ratio will be found a much more reliable index than estimation of the percentage of hemoglobin and the number of erythrocytes.

In secondary anemias associated with dehydration (cachexia, inanition), the cell-plasma ratio being high, the percentage of hemoglobin will be found lower by the new method because the cells have already been concentrated *in vivo*.

These observations suggest a new concept of anemias. Anemias may be divided into:

1. *Cytanemia*: This classification embraces the majority of the types of anemias and is due to a diminution in the number of the red blood cells. It includes secondary and primary (pernicious) anemias. The number of erythrocytes is low, the percentage of hemoglobin is normal or almost so, the color index tends to be high, and the cell-plasma ratio is low (less than 1).

2. *Hemoglobinemia*: This classification includes some secondary anemias and chlorosis. Here the percentage of hemoglobin is low, the number of erythrocytes is normal or increased, the color index is 1 or less and the cell-plasma ratio is 1.

It is interesting to note that in polycythemia vera the percentage of hemoglobin is normal, the number of erythrocytes is greatly increased, the color index is 1 or less and the cell-plasma ratio is high (more than 1).

Some secondary anemias and aplastic anemia fall in an intermediate group between 1 and 2. The foregoing simple classification of anemias

is based on the determination of whether the cells or the hemoglobin are primarily involved. The use of the cell-plasma ratio and the estimation of the hemoglobin content by the cell concentration method appear to be satisfactorily adapted for such a procedure.

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## A SIMPLE METHOD FOR THE ISOLATION OF ANAEROBIC BACTERIA \*

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In this paper I report a simple method of isolation of pure cultures of anaerobic bacteria from blood and other materials from patients.

For the culture of blood, 2 cc. of the citrated specimen is added to a tube containing about 15 cc. of melted agar, and the mixture poured into a Petri dish. After inoculation, the plate is chilled in the icebox until the agar is firm; sterile melted petrolatum is then poured over the surface of the plate to give a layer about 1 cm. in depth. For the culture of surgical swabs, pus and other material, the same procedure is used with the exception that plates are prepared with several different dilutions of the test material to insure obtaining discrete colonies.

The plates are incubated in the usual way.

No difficulty is experienced in the detection of colonies on positive cultures. When it is desired to pick the colonies for transplanting or for staining, the plate is chilled and the hardened layer of petrolatum is easily lifted away with a sterile wooden tongue depressor. If the plate contains gas-formers, it is best to make transplants before the production of gas causes disruption of the culture medium and bubbling of the petrolatum layer.

The simplicity of the method makes possible the inclusion of an anaerobic agar plate as a routine procedure in the culture of all material sent for test to the bacteriologic laboratory of the hospital. It is highly desirable that anaerobic plate cultures should always be included, but the usual methods have required special apparatus or time-consuming procedures that make too great a demand on the resources of the usual hospital laboratory. The method described is as simple as the aerobic plate culture, and at the same time is an effective means of isolating pure cultures of anaerobic bacteria from the infectious material examined in clinical laboratories. During the past three years in the Vanderbilt University Hospital, the anaerobic plates made by this method have frequently shown the presence of anaerobic streptococci and anaerobic bacilli when the aerobic flask cultures and the aerobic plate cultures of the same blood or the same pus have been negative.

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\* Submitted for publication, May 16, 1929.

\* From the Hospital of the Vanderbilt University Medical School.

# General Review

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## THE RETICULO-ENDOTHELIAL SYSTEM IN PROTOZOAN INFECTIONS \*

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The reticulo-endothelial system in relation to the pathogenic protozoa has been the subject of numerous reports. The amount of work on this subject has increased in recent years, particularly as various authors have attempted to analyze more closely the mode of reaction between the body and the infectious organism. The present review has attempted to collect and summarize this work with particular attention to the host's cellular reactions rather than to the activities of the parasite.

Only brief notice can be taken here of the history of the reticulo-endothelial conception and of the morphology of the reticulo-endothelial system. Full accounts of these important points may be found in the reviews to be mentioned.

### HISTORY OF THE RETICULO-ENDOTHELIAL CONCEPTION

Metchnikoff<sup>1</sup> recognized the widespread occurrence throughout the body of a group of closely related cells possessing great phagocytic powers. He designated this group the macrophage system. He included in it not only the reticulum cells of the splenic pulp and the lymph nodes, certain endothelial cells, the Kupffer cells and the large mononuclears of the blood and the lymph, but also the nerve cells, on account of their phagocytosis of lepra bacilli, and the neuroglia cells. The criterion that he used in marking out his macrophage system was the phagocytic power of the cells. It was, indeed, the only criterion then available, since selective dyeing was not yet used. But as Aschoff<sup>2</sup> pointed out, one cannot, on the basis of phagocytosis alone, mark out a special cell system, since probably all cells under the right conditions show their primitive power of phagocytosing and digesting foreign bodies.

Apart from Metchnikoff's work, the early history of the conception of what is now known as the reticulo-endothelial system is the history

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\* Submitted for publication, Sept. 6, 1928.

\* From the Department of Bacteriology, Columbia University College of Physicians and Surgeons.

1. Metchnikoff, E.: *Immunity in Infective Diseases*, New York, G. P. Putnam's Sons, 1905.

2. Aschoff, L.: *Ergebn. d. inn. Med. u. Kinderh.* **26**:1, 1924.

of attempts at vital staining. As early as 1869, Ponfick<sup>3</sup> injected mercury into the lymph sacs of frogs and studied the subsequent distribution of the metal. He failed, however, to differentiate between phagocytosis of particles of the mercury and vital dyeing, which occurs only with colloidal solutions, so that the metal was found in parts of the body that contain none of the reticulo-endothelial system as it is now recognized.

The first to stain the reticulo-endothelial system selectively was Ribbert.<sup>4</sup> He used a colloidal solution of lithium carmine, and showed that after the injection of this material the whole body did not stain, but certain cells only, and that these cells were the same as those that could be filled with hemosiderin and fat.

The study of this cell system received a great impetus with the first use of Ehrlich's vital dyes, particularly pyrrol blue, by Goldmann.<sup>5</sup> This worker was able to correlate the observations of Marchand,<sup>6</sup> Maximow<sup>7</sup> and Renaut,<sup>8</sup> and to show that the large phagocytic cells that they had designated by various names were one and the same. Goldmann was also the first to point out a fact that has come more and more into prominence of late years, namely, that this system plays a rôle in normal metabolism, particularly of glycogen and fat.

Kiyono<sup>9</sup> continued the work on some of the problems that Goldmann raised, especially that as to the origin of the tissue macrophages, or, as he called them, the "histiocytes," in inflammatory processes. At the same time, Aschoff and Landau<sup>10</sup> first used the phrase "reticulo-endothelial system" in a study that they made on the relation of this system to cholesterol. Kiyono, with his pupils, in recent years established the comparative anatomy of the reticulo-endothelial system in all the classes of vertebrates.

Since 1914, a vast literature on the reticulo-endothelial system has grown up, and with it has come a realization of the importance of these cells, not only in pathologic conditions, but in normal metabolism in which their function is probably even more fundamental. Relatively complete summaries of this work are to be found in the reviews of Aschoff,<sup>2</sup> Oberling,<sup>11</sup> Krumbhaar<sup>12</sup> and Sacks.<sup>13</sup>

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3. Ponfick, E.: *Virchows Arch. f. path. Anat.* **48**:1, 1869.

4. Ribbert, H.: *Ztschr. f. allg. Physiol.* **4**:201, 1904.

5. Goldmann, E.: *Beitr. z. klin. Chir.* **64**:192, 1909.

6. Marchand, F.: *Sitzungsb. d. Gesellsch. z. Beford. d. ges. Naturw. zu Marb.* **6**:105, 1897.

7. Maximow, A.: *Arch. f. mikr. Anat.* **67**:680, 1906.

8. Renaut, J.: *Arch. d'anat. micr.* **9**:495, 1907.

9. Kiyono, K.: *Die Vitalekarminspeicherung*, Jena, Gustav Fischer, 1914.

10. Landau, M.: *Ber. d. Naturforsch. Gesellsch. zu Freiburg*, 1913, vol. 20.

11. Oberling, C.: *Ann. d'anat. path.* **1**:87, 1924.

12. Krumbhaar, E. B.: *Internat. Clin.* **2**:280, 1925.

13. Sacks, B.: *Physiol. Rev.* **6**:504, 1926.

## RETICULO-ENDOTHELIAL MORPHOLOGY

Aschoff's definition of the reticulo-endothelial system divides the cells into several categories, the criterion being the intensity with which they take vital dyes in colloidal solution. Thus, four groups are formed, which constitute the reticulo-endothelial system in the wider sense. In a classification slightly modified from that of Aschoff (1924), these groups are: (1) the reticulum cells of the spleen; cortex and medulla strands of the lymph glands; and the other lymphatic tissues; (2) the reticulo-endothelium of the lymph sinuses, blood sinuses, spleen, Kupffer cells, bone marrow capillaries, suprarenal cortex and hypophysis; (3) the histiocytes of the connective tissues (clasmatocytes or tissue macrophages), and (4) the splenocytes and vitally staining monocytes (endothelial leukocytes and blood histiocytes), which arise from the reticulo-endothelium (group 2) and from the histiocytes (group 3).

The cells in groups 2 and 3 stain the most quickly and intensely; those in groups 1 and 4 show somewhat less avidity for the dyes, but their capacity for staining is far greater than that of the fibroblasts and that of the vascular endothelium. The two latter types of cells store dye only slightly after intense and long continued staining of the animal.

The complex interrelations of all these cells cannot be discussed here. They are admirably considered in the reviews mentioned, and also in the articles of Maximow<sup>14</sup> and Foot,<sup>15</sup> which deal specifically with these relations.

## MALARIA

From a careful study of bird malaria, Ben-Harel<sup>16</sup> concluded that the destruction of the parasites is due to the activity of the fixed tissue cells. This process seems to take place principally in the spleen, in which, at the height of the infection, the fixed cells of the endothelial lining are swollen with pigment and parasites. Free parasites are also numerous around the detached monocytes. The blood picture also shows significant changes. The number of monocytes increases directly with the number of parasites, thus showing a response on the part of the reticulo-endothelial apparatus. The actual destruction of parasites by mononuclears in the blood stream appears to be a rare process; however, Ben-Harel, who observed only a single instance of such phagocytosis, stated that the intracellular digestion is so rapid that it cannot often be found.

A similar phagocytosis and destruction of the parasites of malaria in birds had been earlier observed by MacCallum.<sup>17</sup> Thomson,<sup>18</sup> from a

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14. Maximow, A.: *Physiol. Rev.* **4**:533, 1924.

15. Foot, N. C.: *Anat. Rec.* **30**:15, 1925.

16. Ben-Harel, S.: *Am. J. Hyg.* **3**:652, 1923.

17. MacCallum, W. G.: *J. Exper. Med.* **3**:104, 1898.

18. Thomson, D.: *Ann. Trop. Med.* **5**:83, 1912.

study of a large number of cases of malaria in man, concluded that "mononuclear leukocytes, especially the large variety, are undoubtedly the soldiers for defense," in this condition. He observed further that during treatment with quinine, accompanied by a decrease in the number of parasites, there is a corresponding increase in the number of mononuclears; and in contrast with the observations on malaria in birds, he pointed out "that in malarial fever the curve representing the percentage of total mononuclear leukocytes is the exact reverse of the temperature curve."

James,<sup>19</sup> however, considered that the actual appearance in the blood stream of large macrophages (15 microns or more in diameter) is diagnostically more important than any change in leukocytic proportions. Nevertheless, both phenomena are the expression of a response on the part of the reticulo-endothelial mechanism. With still more severe infections, the large "endothelial leukocytes" appear in the blood. Anderson<sup>20</sup> believed that their presence is a sign of a malarial infection of the gravest character, and it is, indeed, evidence of a sharp attack on an important protective mechanism. A similar increase in the large mononuclears in malaria has been reported by Schilling.<sup>21</sup> In one case, he found that 33 per cent were monocytes, and in other cases that frequently from 12 per cent to 30 per cent were monocytes. Christophers and Stephens<sup>22</sup> considered a mononuclear count of 15 per cent or higher as evidence of active malaria. Schilling showed that the cells that are numerically increased in the blood stream during malarial infections correspond with the large monocytes of the spleen, which have probably freed themselves into the blood stream. Histologically, the spleen presents a proliferation of these cells.

In a comprehensive study of malignant malaria, Gaskell and Miller<sup>23</sup> found phagocytosis of the parasites by what they described as the "branched supporting cells" of the spleen and by stellate cells in the liver. The former type of cell is probably the reticulum cell and the latter the Kupffer cell.

In this connection, the observations of McLay<sup>24</sup> are of interest. He studied cultures of *Plasmodium falciparum* and noted that there is a

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19. James, S. P.: Malaria at Home and Abroad, London, William Wood & Company, 1920.

20. Anderson, W. K.: Malarial Psychoses and Neuroses, London, Oxford University Press, 1927.

21. Schilling, C., in Mense, C.: Handbuch der Tropenkrankheiten, Leipzig, Johan Ambrosius Barth, 1924.

22. Christophers and Stephens, cited by McLay, K.: J. Roy. Army M. Corps **38**:93, 1922.

23. Gaskell, J. F., and Miller, W. L.: Quart. J. Med. **13**:381, 1920.

24. McLay, K.: J. Roy. Army M. Corps **38**:93, 1922.

pronounced tendency for the infected erythrocytes to collect about and adhere to the large mononuclears. He confirmed previous workers in the observation that the mononuclears are increased in number as are also their parent cells, the endothelial phagocytes of the internal organs. The clumping of the infested erythrocytes around the mononuclears may possibly be the result of a positive chemotaxis, and the increase in the number of the mononuclear cells in the culture films during the process of cultivation suggests that they may be connected with the dying out of the parasites. He further concluded that these cells are an important part of the body's defenses against *Plasmodium falciparum*. Commenting on this work, Wenyon<sup>25</sup> pointed out that it is probable that in infections with *Plasmodium falciparum*, which have been latent for a long period, the cycle of development is continuous in the vicinity of the cells to which the parasites tend to cling, namely, in the spleen and the bone marrow.

Much of the work that has been reviewed here suggests the possibility that immunity to malaria, slight though it be, arises from the activity of the reticulo-endothelial system. At least, there can be no doubt that the cells of this system play an outstanding part in the obvious defense processes of the body, such as phagocytosis; it is to them that one would be inclined to look for the origin of the less easily analyzed phenomena of immunity to malaria.

Recently, Ruge<sup>26</sup> made the interesting suggestion that the constant presence of malarial pigment in the cells of the reticulo-endothelial system prevents the production of immunity to malaria. The pigment is thought to act as a "blocking" material, analogous to india ink or trypan blue. Such a hypothesis must be received with caution, since experimental results from a blockade are well known to be extremely variable, particularly in cases in which the formation of antibodies is involved.

A diagnostic test for malaria that indirectly involves the reticulo-endothelial system was devised by Kingsbury.<sup>27</sup> He pointed out that this system normally breaks hemoglobin into bilirubin and that the amount of bilirubin is increased in cases in which the destruction of erythrocytes is increased, as in malaria. He found that, under treatment with quinine, the amount of bilirubin in the serum decreases. Kingsbury advocated the determination of the amount of bilirubin in the serum as a test for malaria.

None of the other sporozoan parasites found in man has been noted in connection with the reticulo-endothelial system. Observations have been made, however, that certain of the hemogregarines of the lower

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25. Wenyon, C. M.: Protozoology, London, William Wood & Company, 1926.

26. Ruge, R.: Med. Welt **1**:2, 1927.

27. Kingsbury, A. N.: Tr. Roy. Soc. Trop. Med. & Hyg. **20**:359, 1927.

mammals pass at least part of their life cycle in the cells of this system. These observations may be briefly reviewed. Patton,<sup>28</sup> in 1906, described a hepatozoon within the mononuclear leukocytes of an Indian palm squirrel. In infected animals, the mononuclear leukocytes averaged 60 per cent, while in normal, noninfected animals these cells averaged 28 per cent. The proportion of mononuclears was higher in the more heavily infected animals. Christophers<sup>29</sup> and Wenyon<sup>30</sup> found that the schizogony cycle of *Hepatozoon canis* takes place in mononuclear cells of the spleen and the bone marrow, while the gametocytes occur in the circulating mononuclears. The blood monocytes harbor the gametocytes also in *Hepatozoon perniciosum* infestations of the rat, according to Kasuma, Kasai and Kobayashi.<sup>31</sup> The latter form, which was reported by Miller<sup>32</sup> in 1908, was described as having schizonts exclusively in the liver cells. Wenyon,<sup>25</sup> however, was of the opinion that the schizonts may in reality be in the Kupffer cells. If so, the entire mammalian cycle occurs in cells of the reticulo-endothelial system.

#### KALA-AZAR

Kala-azar is apparently an example of a primary and chronic infection of the reticulo-endothelial system. In the earliest careful description of the disease, Christophers<sup>33</sup> emphasized the intracellular position of the parasites. They were present in the endothelial cells or macrophages not only in the liver and the spleen, but most strikingly in the intestinal wall, where they occupied the interior of the macrophages, in the granulation tissue which had replaced the mucosa. He also pointed out the characteristic infiltration of various organs with macrophages, particularly the liver, the spleen and the bone marrow. These changes were recently studied by Meleney,<sup>34</sup> who found that the proliferation and infiltration of macrophages in these organs may be so great as to fill the greater part of each of them. In extreme cases, the connective tissue clasmatoocytes of almost all the organs and tissues are infested.

Further work by two English investigators, Shortt<sup>35</sup> and Perry,<sup>36</sup> clearly showed kala-azar to be essentially a disease of the reticulo-endothelium. Shortt, who studied the disease experimentally in two monkeys,

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28. Patton, W. S.: Scient. Mem. Med. Off. India, Calcutta, 1906, no. 24.

29. Christophers, S. R.: Scient. Mem. Med. Off. India, Calcutta, 1906, no. 26.

30. Wenyon, C. M.: Parasitol. 4:273, 1911.

31. Kasuma, S.; Kasai, K., and Kobayashi, R.: Kitasato Arch. Exper. Med. 3:103, 1919.

32. Miller, W. S.: Bull. Hyg. Lab., U. S. P. H. S., 1908, no. 46.

33. Christophers, S. R.: Scient. Mem. Med. Off. India, Calcutta, 1904, nos. 8 and 11.

34. Meleney, H. E.: Am. J. Path. 1:147, 1925.

35. Shortt, H. E.: Indian J. M. Research 11:186, 1923-1924.

36. Perry, H. M.: J. Roy. Army M. Corps. 39:323, 1922.



stated that the parasites are confined to one special tissue of the body, and this tissue is endothelium. Perry investigated intestinal infections with *Leishmania donovani* and found that the interiors of many villi in the small intestine were replaced and filled with large macrophages loaded with parasites. He believed that these macrophages arise from the lymphatic endothelium of the central lacteals in each villus.

Important contributions have recently been made to the subject of kala-azar in its relation to reticulo-endothelium by a group of workers in Peking. Young, Smyly and Brown<sup>37</sup> discovered that the Chinese hamster (*Cricetulus griseus*) is an excellent animal for use in the experimental production of this disease. In their brief report, they made record that the enlarged spleen is the only gross pathologic change that this animal shows. Later, Meleney, in his thoroughgoing study of kala-azar in the hamster and the monkey, as well as in man, reported that the two main features of the disease in all these animals are: (1) an extensive proliferation of endothelial cells in the liver, the spleen and the bone marrow (that is, the reticulo-endothelium) and (2) the formation of large islands of such cells (clasmatocytes) in these organs. These cells are selectively infested by *Leishmania donovani*.

The next contribution was made by Hu and Cash,<sup>38</sup> who by means of vital and supravital staining proved conclusively the reticulo-endothelial character of the infested cells. When they injected china ink, which has a specific affinity for this system, into an animal infected with *Leishmania*, they found that the ink was taken up by the cells that contained the parasites. The infested cells were obtained for supravital staining by puncture of the spleen, and their reaction to the dye showed that they were clasmatocytes.

They also noted the interesting fact that large numbers of the parasites are to be found in clasmatocytes lying in various layers of the skin. In another report,<sup>39</sup> they showed that much the same condition is present in the human skin, in which again it is the clasmatocytes that contain the parasites.

Further evidence of the involvement of the reticulo-endothelium in man is found in a study of 400 cases of visceral leishmaniasis in Spaniards made by Pittaluga.<sup>40</sup> He concluded that the disease is one of blockage of the reticulo-endothelial apparatus. To this blockage, he attributed the symptoms of the disease: anemia, leukopenia, splenomegaly and hepatomegaly and cutaneous hemorrhages.

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37. Young, C. W.; Smyly, H. J., and Brown, C.: Proc. Soc. Exper. Biol. & Med. **21**:357, 1924.

38. Hu, C. H., and Cash, J. R.: Proc. Soc. Exper. Biol. & Med. **24**:469, 1927.

39. Cash, J. R., and Hu, C. H.: Kala-Azar; Demonstration of *Leishmania Donovanii* in the Skin and Subcutaneous Tissue of Patients; Possible Relation to the Transmission of the Disease, J. A. M. A. **89**:1576 (Nov. 5) 1927.

40. Pittaluga, G.: Arch. f. Schiffs- u. Tropen-Hyg. **21**:340, 1927.

Not all workers, however, have found *L. donovani* exclusively in the cells of this system. Laveran and Havet<sup>41</sup> described the liver cells of an experimentally infected dog as more heavily infested than the Kupffer cells. Shortt could not confirm this in his work on monkeys, and such heavy infestation has not been found by other workers, although a slight infection of liver cells has been reported elsewhere, as, for example, in Meleney's paper. *Leishmania* is also found occasionally in polymorphonuclear cells. These occasional and, in part, unconfirmed results do not weaken the main trend of the other observations; namely, that kala-azar is a disease which primarily attacks the reticulo-endothelial system.

As might be expected from the nature of the disease, the numerical proportions of the blood cells are changed in kala-azar. Schittenhelm<sup>42</sup> described a leukopenia with a considerable increase in the proportion of mononuclears. The cell percentages vary considerably with different authors. Knowles<sup>43</sup> found the percentage of these cells ranging from 6 to 40. Rogers<sup>44</sup> found mononuclear counts of over 12 per cent in 69 per cent of the cases that he studied, while Donovan<sup>45</sup> obtained an average of 23 per cent.

The protozoons classed as *Leishmania*, other than *L. donovani*, show a similar tendency to invade the macrophages. The first observation of tissue macrophages in the oriental sore seems to have been made by Riehl<sup>46</sup> in 1886, although the parasites themselves (*L. tropica*) were seen by Cunningham<sup>47</sup> in the previous year. The first thorough report on the cells did not appear until 1903; in that year Wright<sup>48</sup> noted that the great majority of the organisms occur in the lesions within cells that are undoubtedly clasmatoocytes. The principal part of the infiltration that he observed was due to cells of this type; this has been confirmed by numerous workers. Interesting cases of dermal leishmanoid infections that appeared in patients undergoing treatment for kala-azar were reported by Shortt and Brahmachari.<sup>49</sup> The parasites (*L. donovani*) occurred subcutaneously within masses of cells, which, from the careful descriptions and the photomicrographs, were, without doubt,

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41. Laveran, A., and Havet, J.: Bull. Soc. de path. exot. **10**:396, 1917.

42. Schittenhelm, A.: Handbuch der Krankheiten des Blutes, Berlin, Julius Springer, 1925.

43. Knowles, R.: Indian J. M. Research **8**:140, 1920.

44. Rogers, L.: Fevers in the Tropics, London, H. Frowde, Hodder & Stoughton, 1908.

45. Donovan, C., cited by Schittenhelm (footnote 42).

46. Riehl, G.: Vrtljschr. f. Derm. u. Syph., 1886, p. 805.

47. Cunningham, D. D.: Scient. Mem. Med. Off. India, Calcutta **1**:21, 1885.

48. Wright, J. H.: J. M. Research **10**:472, 1903.

49. Shortt, H. E., and Brahmachari, U. N.: Indian J. M. Research **12**:463, 1925.

tissue macrophages. Recently, Llambias and Mosto<sup>50</sup> pointed out that in a case of American dermal leishmaniasis the mononuclear cells were the most prevalent type.

#### EXPERIMENTAL TRYPANOSOMIASIS

It is becoming increasingly evident that in many experimental infections with trypanosomes, the reticulo-endothelial system is not directly involved. Laveran and Mesnil<sup>51</sup> described an intraperitoneal phagocytosis of *T. lewisi* by large mononuclear cells; but their observations could not be confirmed by MacNeal<sup>52</sup> nor by Manteufel.<sup>53</sup> Dwijkoff,<sup>54</sup> in a careful hematologic study of guinea-pigs infected with *T. brucei*, never observed a mononuclear count greater than 6 per cent, and concluded that a reaction of the reticulo-endothelial system had not occurred. Linton,<sup>55</sup> working with splenectomized guinea-pigs infected with *T. equiperdum*, did not find any differences in respect to incubation period or length of life between these animals and nonsplenectomized controls, showing that the absence of this important portion of the apparatus did not have any effect on the course of the disease.

In some instances, however, notably in the results of Rosenthal and of Taliaferro, which will be discussed later, this apparatus has been found responsible for immunity in infections with trypanosomes, although only indirectly.

*The Trypanocidal Action of Serum from Human Beings.*—Rosenthal began with the observation of Laveran<sup>56</sup> that serum from normal human beings is trypanocidal when injected into mice infected with *T. brucei*, *T. evansi* or *T. equiperdum*. In collaboration with Nossen<sup>57</sup> and later with Kreuger,<sup>58</sup> Rosenthal noted that in the case of certain severe disturbances of the liver, such as cancer with icterus, the trypanocidal power of serum from human beings, as shown by injection into infected mice, is weakened and may even disappear. From their work, they concluded that the trypanocidal substance is a secretion of the liver. This conclusion was confirmed by Peutz,<sup>59</sup> Neumark and Pagorschelsky<sup>60</sup> and others.

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50. Llambias, J., and Mosto, D.: Compt. rend. Soc. de biol. **95**:823, 1926.

51. Laveran, A., and Mesnil, F.: Ann. de l'Inst. Pasteur **15**:673, 1901.

52. MacNeal, W.: J. Infect. Dis. **1**:517, 1904.

53. Manteufel: Arb. a. d. k. Gsndhtsamte **33**:46, 1909.

54. Dwijkoff, P.: Folia haemat. **33**:1, 1926.

55. Linton, R. W.: Unpublished experiments.

56. Laveran, A.: Compt. rend. Acad. d. sc. **134**:735, 1902.

57. Rosenthal, F., and Nossen, H.: Berl. klin. Wchnschr. **58**:1093, 1921.

58. Rosenthal, F., and Kreuger, M.: Berl. klin. Wchnschr. **58**:382, 1921.

59. Peutz, J. L. A.: Nederl. Tijdschr. v. Geneesk. **66**:1544, 1922.

60. Neumark, E., and Pagorschelsky, H.: Ztschr. f. Kinderh. **40**:535, 1925.

Later research by Rosenthal and Freund <sup>61</sup> repeated the earlier observations and added several important points to them. The trypanocidal substance is present in the euglobulin and pseudoglobulin fractions of serum from man. It does not have antigenic power in rabbits and mice; that is, an antitrypanocidal substance is not formed by the injection of serum from human beings into these animals. The repeated injection of small amounts of this serum into a mouse renders a subsequent injection for protective purposes ineffectual. Since the repeated injections do not cause the formation of an antitrypanocidal substance and from the further consideration that serum from human beings is inactive *in vitro*, Rosenthal and Freund were led to the hypothesis that this serum does not act directly to kill the trypanosomes, but is first activated by some element of the mouse body. Thus, the ineffectiveness of serum from human beings in mice into which it has been injected repeatedly is due to an exhaustion of the mechanism for its activation. As a corollary to this hypothesis, one must assume that the natural immunity which man shows against animal trypanosomes is not due to the trypanocidal action of his serum, as was once supposed, but depends on some other mechanism.

In a final report, Rosenthal and Spitzer <sup>62</sup> completed the work in a study of the mechanism whereby serum from human beings is activated in mice. They showed first that treatment of animals with thorium-X resulting in almost total destruction of the circulating leukocytes, did not prevent a complete activation of this serum. Their further experiments were on the activity of the reticulo-endothelial system. In mice treated with saccharated iron oxide, which is taken up selectively by the cells of this system, they obtained an inconstant but often pronounced lowering of the trypanocidal power, followed in some cases by the death of the animal. The saccharated iron oxide itself did not render serum from human beings incapable of being activated. In other experiments, they extirpated the spleen, which in mice forms a higher proportion of the reticulo-endothelial system than in other animals, and found that little activation of the serum from man took place. That is, the splenectomized animals frequently died of the trypanosome infections. The controls given similar doses of trypanosomes and of the serum were completely protected. Finally, it was found that blocking, combined with splenectomy, was invariably fatal.

From these experiments, the authors concluded that the serum of human beings, which is inactive *in vitro*, becomes trypanocidal in the mouse through its activation by the reticulo-endothelial system. These important researches have clearly demonstrated the importance of the

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61. Rosenthal, F., and Freund, R.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **37**:48, 1923.

62. Rosenthal, F., and Spitzer, F.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **40**:529, 1924.

tissues in a certain type of protection against protozoan infections, namely, protection due to an activation of a foreign substance, whether serum or drug, by the body cells.

The results of several earlier experimenters find their explanation in this work of Rosenthal. Thus Laveran and Mesnil<sup>63</sup> noted that the usual energetic action of the serum of human beings against *T. brucei* in mice failed after several injections, and the animals succumbed. The same phenomenon was observed by Jacoby<sup>64</sup> and by Leboef.<sup>65</sup> In the light of Rosenthal's work, it is clear that by means of their repeated injections these workers had exhausted the activating power of the mouse reticulo-endothelium for the serum of man.

*Reticulo-Endothelium and the "Reaction-Product" of Taliaferro.*—In a series of papers, Taliaferro<sup>66</sup> described a new type of resistance in rats infected with the nonpathogenic *T. lewisi*. This resistance manifests itself in an inhibition of mitosis, so that the organisms after several days cease to divide. Their eventual disappearance, Taliaferro believed, is due to lysis, a phenomenon entirely separate from the inhibition of reproduction. The "reaction product" that inhibits reproduction may be transferred in the serum from an infected rat to a normal rat, and prevent the organisms from showing any reproduction in the latter animal.

The existence of this property was confirmed by Coventry<sup>67</sup> and by Regendanz and Kikuth.<sup>68</sup> The former studied particularly the titer of the "reaction product" at various stages during the infection and found that, while it could not be demonstrated on the fifth day of the infection when reproduction had begun to decrease, it appeared explosively on the sixth day in large amount and gradually increased until about the thirty-fifth day, when it again diminished.

Interesting from the present point of view is the confirmation of Taliaferro's results by Regendanz and Kikuth. They splenectomized rats and infected them with *T. lewisi*. In these animals, numerous dividing forms could be found for two or three days longer than in nonsplenectomized controls, and in some cases the infections terminated fatally, without the appearance of any product inhibiting reproduction. Hence, they believed that the spleen is the important site of the formation of Taliaferro's "reaction product," and, on the basis of the work of others on the formation of antibodies, concluded further that the reticulo-endothelial apparatus is involved.

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63. Laveran, A., and Mesnil, F., cited by Schilling, in Kolle and Wassermann: Handb. d. pathogenen Mikroorganismen, Jena, Gustav Fischer, 1927, vol. 8, p. 95.

64. Jacoby, M.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**:689, 1909.

65. Leboef, A.: Ann. de l'Inst. Pasteur **25**:882, 1911.

66. Taliaferro, W. H.: Am. J. Hyg. **3**:104, 1923; J. Exper. Med. **39**:171, 1924.

67. Coventry, F. A.: Am. J. Hyg. **5**:127, 1925.

68. Regendanz, P., and Kikuth, W.: Zentralbl. f. Bakteriologie **103**:271, 1927

*The Reticulo-Endothelial System and Chemotherapeutic Activity.*—It has been known for years that many chemotherapeutic substances have a much greater activity against protozoa in vivo than in vitro, some of them indeed being without parasitidal action in the test tube. For example, Oettinger<sup>69</sup> found that while solutions of neoarsphenamine in dilution of 1:3,000 are inactive in vitro, in the body, in which their concentration may be only 1:70,000 or 1:80,000, they show a strong parasitidal action.

The exact mode of action of chemotherapeutic substances is still a matter of experiment and controversy. It is agreed, however, that with many drugs the body does not take a passive part, but either elaborates the drug into an effective parasitidal substance, or is stimulated by it to form or to set free parasitidal antibodies. The experiments of Schilling and Jaffé<sup>70</sup> pointed to the latter possibility. Three hours after the injection of arsenophenylglycine into a rabbit infected with *T. brucei*, 1 cc. of its serum, which had previously been inactive, was able to lengthen the period of incubation in a mouse infected with the same organism to thirteen days and to prolong its life to the sixteenth day. They believe that the circulating drug itself does not cause this increased trypanocidal power, for 0.5 cc. of rabbit serum taken nine days after the last injection of the drug protected a mouse. They account for the rapid appearance of the antibodies in the rabbit's blood on the hypothesis that these substances are already formed in the tissue cells and are released by the action of the arsenophenylglycine.

While discrepancies between activity in vitro and that in vivo have long been recognized, it is only recently that a closer analysis, from a cellular point of view, has been attempted. Studies in this direction were reported in three papers, which appeared almost simultaneously, by Jungeblut,<sup>71</sup> Feldt and Schott<sup>72</sup> and Kritschewsky and Meersohn.<sup>73</sup> The methods in all were essentially the same. White mice were splenectomized, or were given injections of some kind of "blocking" material, such as saccharated iron oxide or india ink; or were treated in both ways. The animals were then infected, together with normal controls, with the spirochete of recurrent fever or with *T. brucei*. In some of the experiments of Feldt and Schott, a streptococcus was used. After infection, they were treated with various chemotherapeutic substances,

69. Oettinger, J.: Ztschr. f. klin. Med. **103**:546, 1926.

70. Schilling, C., and Jaffé, J.: Arch. f. Schiffs- u. Tropen-Hyg. **13**:525, 1909.

71. Jungeblut, C. W.: Ztschr. f. Hyg. u. Infektionskrankh. **107**:357, 1927.

72. Feldt, A., and Schott, A.: Ztschr. f. Hyg. u. Infektionskrankh. **107**:453, 1927.

73. Kritschewsky, I. L., and Meersohn, I. S.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:407, 1926.

and the subsequent course of the infection was compared with that in the controls. In every case, it was found that the splenectomized and blocked mice showed severer infections and a mortality much higher than the control mice. Jungeblut found a death rate of 62 per cent in the splenectomized and blocked animals as compared with one of 11 per cent in the controls. Kritschewsky and Meersohn obtained figures of 75 per cent and 10 per cent, respectively. Jungeblut concluded that "the full action of chemotherapeutic substances in protozoan infections of mice appears in general to depend upon the presence of an intact reticulo-endothelial system." The conclusions of the other authors were essentially the same.

In subsequent studies, Kritschewsky<sup>74</sup> tested a large series of drugs in a way similar to that described. Without exception, the activity of the drugs was lessened or abolished after splenectomy, either alone or combined with blocking. This worker's view is that, since the drug cannot enter the reticulo-endothelial cells, it is rapidly excreted. The intracellular occurrences are not known, but Kritschewsky believed it is possible that there a metamorphosis of the drug into its active form takes place.

Using similar materials and technic, Kolpikow<sup>75</sup> tested the response of mice to drugs at varying intervals after splenectomy. He concluded that there was a gradual replacement of the spleen by other cells in the function of drug activation, since the longer after splenectomy the dose was given, the better was the response. After about fifty days, the amount of activation was almost as good as in nonsplenectomized animals.

Kligler and Weitzman<sup>76</sup> discovered an important further interaction between a drug and the reticulo-endothelial apparatus. Animals cured by Bayer 205 of an otherwise fatal infection with *T. evansi* developed a resistance to reinfection, which lasted about five months. They believed that this resistance is cellular in character, because humoral antibodies could not be demonstrated and because blocking of the reticulo-endothelial system with oil caused a disappearance of the resistance.

Later Kligler<sup>77</sup> reported that animals cured and made resistant to *T. evansi*, as in the earlier work, are also insusceptible to reinfection with *T. gambiense* for about the same period.

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74. Kritschewsky, I. L.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**: 506, 1927.

75. Kolpikow, N. W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **48**:182, 1926.

76. Kligler, I. J., and Weitzman, I.: Proc. Soc. Exper. Biol. & Med. **23**:355, 1926.

77. Kligler, I. J.: Ann. Trop. Med. **22**:21, 1928.

## SUMMARY

While conclusions are not to be drawn from this review, it is apparent that as a more thorough insight into the course of protozoan infections has been gained, the tissue cells of the host have assumed a correspondingly greater importance. A direct action of these cells is shown in malaria and in kala-azar and an indirect action in some of the experimental infections with trypanosomes and in chemotherapeutic action. Whether the responses of the animal body to protozoan infections will prove to be qualitatively different from those to the bacterial diseases, which have been much more deeply investigated, is a question that future research will decide. There is evidence, however, especially in the work of Taliaferro and of Rosenthal, that different types of response do occur in protozoan infections.



## Notes and News

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**University News, Promotions, Registrations and Appointments.**—At Columbia University, New York, Frederick B. Humphreys has been made associate professor of bacteriology, and Maurice N. Richter and Theodore F. Zucker, assistant professors of pathology.

In the School of Medicine, Western Reserve University, Cleveland, Alan Moritz has been promoted to be assistant professor of pathology; David Seecof has been appointed assistant professor of pathology, and LaVerne Barnes, senior instructor in bacteriology and hygiene; Howard T. Karsner, professor of pathology since 1914, has been given the additional title of director of the Institute of Pathology which has just been completed.

Burrell O. Raulston, at one time instructor in pathology at Rush Medical College, Chicago, has been appointed professor of medicine in the University of Southern California.

Frederick Eberson has been appointed director of the laboratories of the Mount Zion Hospital, San Francisco.

At the University of Cincinnati, Pearl M. Zeek has been made instructor in pathology. Pearl M. Zeek and Irving H. Schroth have been appointed assistant visiting pathologists to the Cincinnati General Hospital.

In the School of Medicine, St. Louis University, William D. Collier has been made director of the department of pathology and John R. Roberts has been promoted to senior instructor in pathology.

Detlev W. Bronk has been appointed Johnson professor of biophysics in the University of Pennsylvania School of Medicine and director of the Johnson Foundation for Research in medical physics.

Aldo Perroncito, professor of general pathology in the University of Pavia since 1921, succeeding his uncle, Camillo Golgi, has died at the age of 46.

Edward C. Streeter has been appointed visiting professor of the history of medicine in the medical school of Yale University.

John F. Kessel has been appointed associate professor of bacteriology and parasitology in the school of medicine of the University of Southern California.

At the University of Chicago, Isidore S. Falk has been promoted to a full professorship in bacteriology and hygiene.

After about thirty-two years of service, Timothy Leary has resigned as professor of pathology, bacteriology and medical jurisprudence in Tufts College Medical School, Boston.

Allan W. Blair has been appointed instructor in pathology and bacteriology in the University of Alabama.

Veranus A. Moore, dean of the college of veterinary medicine, concludes this year a teaching career of thirty-three years at Cornell University. He was a member of the first veterinary faculty as professor of veterinary pathology and bacteriology in 1896, and in 1908 became dean of the college.

Kiyoshi Hosoi, recently of the department of physiology, Mayo Foundation, Rochester, Minn., has been appointed senior Littauer fellow in pathology at the Albany Hospital and Medical College; and Edward H. Crosby of the department of surgery, University of Chicago, junior Littauer fellow in pathology.

Yolande de la Pasture, instructor in pathology at the Albany Medical College, has resigned to accept a residency in pediatrics at the Boston Dispensary, Boston, Mass.

Arthur H. Dodge, ex-Lieutenant Commander, U. S. Navy, and pathologist at the Grasslands Hospital, Valhalla, N. Y., has died at the age of 51.

The medical fellowship board of the National Research Council has made the following reappointments for the year 1929-1930: Simon Dworkin, physiology; Stephen J. Maddock, experimental surgery; Kenneth I. Melville, pharmacology

and physiology; Valy Menkin, physiology; David McK. Rioch, neurophysiology, and Ethel D. Simpson, physiology. New appointments are: Edgar V. Allen, internal medicine; Eric G. Ball, physiological chemistry; Claude H. Forkner, pathology and clinical investigation; Emidio L. Gaspari, bacteriology and immunology; Arthur K. Koff, obstetrics; Milton Levy, biochemistry; Ava J. McAmis, physiological chemistry; Leone McGregor, pathology; Charles Midlo, anatomy, and Bruce Webster, internal medicine.

The Rockefeller Institute for Medical Research announces the following appointments and promotions to the scientific staff. Associates appointed are: Albert P. Krueger, A. L. Patterson and Oskar Seifried. Assistants are: Alf S. Alving, Frank H. Babers, Bernard Benjamin, George P. Berry, Robert T. Dillon, Samuel E. Hill, William H. Kelley, Franklin R. Miller, Clara Nigg, Merritt P. Sarles, Maxwell P. Schubert, Mark P. Schultz, Albert B. Scott, J. Murray Steele, Jr., Philip G. Stevens, Bettina Warburg and Bruce K. Wiseman. Assistants who are made associates are: Lawrence R. Blinks, Louis A. Julianelle, Philip Levine, John B. Nelson, Theodore Shedlovsky and Harold J. Stewart.

Ralph E. Miller, Hanover, N. H., and Harold C. Thornton, Ferrum, Va., have been assigned as fellows of the Mayo Foundation, Rochester, Minn., and will major in pathology.

**Burdick Research Award.**—Walter M. Simpson, director of the diagnostic laboratories of the Miami Valley Hospital, Dayton, Ohio, was the first recipient of the Ward Burdick Research Award (gold medal) at the recent meeting of the American Society of Clinical Pathologists, at Portland, Ore., in recognition of his researches in tularemia and undulant fever. At the meeting of the American Medical Association, at Minneapolis, in 1928, Dr. Simpson was awarded the gold medal (class II) for his exhibit of the gross and microscopic changes in tularemia. The late Ward Burdick, of Denver, was instrumental in organizing the American Society of Clinical Pathologists eight years ago. He died in 1928. It is the purpose of the society to perpetuate his memory by the presentation of an annual research award to the member of the society who has made an outstanding contribution to medical research.

**Committee on Gases in Refrigerators.**—The American Medical Association has appointed the following committee to report on the danger of intoxication from the use of gases such as methyl chloride in household refrigerators: H. Gideon Wells, R. L. Thompson, Casey P. McCord, Yandell Henderson and Paul N. Leech.

**Kober Medal.**—The Kober medal of the Association of American Physicians for 1929 has been awarded to George R. Minot, Boston, for his work on the treatment of pernicious anemia.

**Cooperative Research in Dental Physiology and Pathology.**—The Rockefeller Foundation has made a grant to the medical school of Yale University toward the intensive study of the physiology and pathology of the teeth. Milton C. Winternitz is the chairman of the group of scientists in different fields in charge of the work.

**New York Lying-In Hospital.**—Frederick A. Hemsath has been appointed pathologist. He resigns as director of the Cattaraugus County Laboratory, New York.

**American Society of Clinical Pathologists.**—At the annual meeting in Portland, Ore., on July 8, James H. Black, Dallas, Texas, was made president, and Kenneth M. Lynch, Charleston, S. C., president-elect. Harry J. Corper, Denver, continues to be secretary-treasurer.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

EXPERIMENTAL PERICARDITIS. GEORGE HERRMAN and J. H. MUSSER, *Am. Heart J.* **4**:268, 1929.

Various types of chronic fibrous pericarditis can be reproduced at will in dogs. The animals may show no pathologic clinical signs, and the electrocardiographic observations may be negative, but the fluoroscope will often reveal significant changes in the character and movements of the left border of the heart. The greatest degree of cardiac hypertrophy is found in those cases in which chronic mediastinal and peritoneal adhesions accompany the adhesive pericarditis. The feasibility of digital separation of pericardial adhesions and the prevention of reformation of adhesions have been proved, and clinical and pathologic evidence of benefit has been noted in animals.

PEARL ZEEK.

MYXEDEMA HEART. JACOB EASTMON HOLZMAN, *Am. Heart J.* **4**:351, 1929.

Myxedema heart is characterized by an enlargement of all four chambers, slow pulse rate, normal blood pressure and electrocardiographic changes. Two groups are recognized: those cases which respond to thyroid therapy, and those in which myxedema of long standing and other factors have produced permanent myocardial changes which do not permit a response to thyroid medication.

PEARL ZEEK.

THE DIAGNOSIS OF EARLY PREGNANCY THROUGH THE DETECTION OF FEMALE SEX HORMONE IN THE URINE. CHARLES MAZER and JACOB HOFFMAN, *Am. J. Obst. & Gynec.* **17**:186, 1929.

Carefully selected castrated mice (two for each test) were injected with 20 minims of urine for five consecutive intervals of two hours. The urine was obtained from pregnant and control nonpregnant women. The production of estrus-like changes in the vaginal smear of the mice, by the pregnant urine only, was considered as positive evidence of the presence of female sex hormone in the urine and diagnostic for pregnancy. The contradictory observations of Frank and Goldberg showing an absence of this hormone in the blood of early pregnancy are explained by Mazer and Hoffman by assuming that there is possibly an increased renal permeability for the hormone which depletes the blood of its presence, but later, when the placenta supplements the function of the corpus luteum of pregnancy, large quantities of sex hormone appear in the blood apparently more than the kidneys can filter through.

A. J. KOBAK.

RHYTHMIC VARIATIONS IN THE VASCULARITY OF THE UTERUS OF THE GUINEA PIG DURING THE ESTROUS CYCLE. J. E. MARKEE, *Am. J. Obst. & Gynec.* **17**:205, 1929.

Three methods were utilized in studying cyclic variations that occur in the guinea-pig uterus. The first method consisted in opening the abdominal cavity and studying the gross and microscopic changes of the uterus in situ; a wave of light area was seen every minute to spread over the red uterus from the horns down to the cervix and lasted about ten or fifteen seconds. The second method consisted in studying transplants of endometrial tissue in the anterior chamber of the eye. The transplanted tissue underwent vascular changes which varied between 0 and 50 per cent on the Talquist hemoglobinometer. Kymographic records were made of the color changes by means of a graduated dial and a muscle lever. "These vascular changes are influenced by the time of the day, being at their lowest ebb

in the early morning, increasing both in speed and extent in the forenoon, decreasing again about noon, and reaching their height late in the evening. They are influenced by the stage of the estrous cycle, showing during proestrous until they disappear completely for four or five hours and then to reappear before the end of the period of heat." The third method consisted in inserting a speculum 4 mm. in diameter through the vagina and half way up one of the horns of the uterus. By this procedure the observations made by the first two methods were confirmed in that the endometrium changed from red to white and back again from every fifteen to twenty seconds during diestrus, but not during estrus. The author concludes that the vascular changes are a phenomenon of the capillaries and arterioles of the uterus and especially of the mucous membrane.

A. J. KOBAK.

EXPERIMENTAL ENDOMETRIOSIS. S. S. SCHOCHET, *Am. J. Obst. & Gynec.* **17**: 328, 1929.

The cyclic variations of the endometrium in situ and when transplanted into other organs were studied and described by Schochet, who first used rabbits and later only virgin female guinea-pigs. The vessels of the transplants showed periodic rhythmic contractions, which were described by Markee who collaborated with Schochet on this phase of the work. These rhythmic variations consisted of an alternate blanching and blushing of the uterus in situ, and when endometrial tissue was transplanted into the anterior chamber of the eye, further cyclic variations were noted in the alternate changes of color which varied with the time of the day as well as the time of the estrous period that it was observed. A Tallquist scale was used for studying the degree of the color changes which occurred during the pro-estrous period, disappeared during the estrous period, and reappeared shortly after the postestrous period began. The experimental transplants were divided as follows: Series 1 consisted of normal controls removed during the pro-estrous period and transplanted into the spleen, liver and subcutaneous tissue; a second group of these controls was removed at varying periods and transplanted into the anterior chamber of the eye. Series 2 consisted in an observation of transplanted endometrium after the tissues had been subjected to lipid solvents. In series 3, the tissues were first subjected to solutions of iso-osmotic strontium chloride followed by a change into hypertonic salt solution, and then washing in Ringer's solution before transplanting into the anterior chamber of the eye.

A. J. KOBAK.

RELATION OF SPRUE TO PERNICIOUS ANEMIA. AMERICO SERRA, *Am. J. Trop. Med.* **9**:49, 1929.

Pernicious anemia and sprue are two distinct disease entities. Important points of differentiation between the two diseases are emaciation, lack of fat utilization and small liver in sprue spinal cord changes, achlorhydria and fever in pernicious anemia. The icteric index is high in uncomplicated cases of pernicious anemia, while that in cases of sprue ranges within normal limits. Nitrogen retention is usually absent in sprue although common in pernicious anemia. The blood picture in the two diseases is similar. A high color index, macrocytosis and leukopenia with relative lymphocytosis are common to sprue and pernicious anemia. Polychromatophilia, anisocytosis, poikilocytosis and basophilic stippling are more marked in pernicious anemia. Nucleated red cells are rare and the reticulated cell counts are lower in sprue. The blood picture of sprue is of a more aplastic type than that of pernicious anemia.

H. E. LANDT.

THE RELATION OF OVARIES AND TESTES TO CHOLESTEROL METABOLISM. F. S. RANDLES and A. KNUDSON, *J. Biol. Chem.* **82**:57, 1929.

Experiments are described showing that removal of the testes from male or the ovaries from female rats has no appreciable effect on the cholesterol content of the blood.

AUTHORS' SUMMARY.

THE NEPHROPATHOGENIC ACTION OF CYSTINE. G. J. COX, C. V. SMYTHE and C. F. FISHBACK, *J. Biol. Chem.* **82**:95, 1929.

Very young rats manifest acute toxic nephrosis when restricted to synthetic diets containing from 0.3 to 0.9 per cent of the sulphur-containing amino-acid, cystine. Survival of the period of acute nephrosis appears to be associated with the development of a tolerance for the substance. Older rats are insusceptible.

ARTHUR LOCKE.

THE RÔLE OF THE PHOSPHOLIPIDS OF THE INTESTINAL MUCOSA IN FAT ABSORPTION. R. G. SINCLAIR, *J. Biol. Chem.* **82**:117, 1929.

The transformation of absorbed fatty acid into phospholipid may be an essential step in the resynthesis of neutral fat within the epithelial cells of the intestinal mucosa.

ARTHUR LOCKE.

THE FATE OF COLLOIDAL IRON ADMINISTERED INTRAVENOUSLY. CYRIL J. POLSON, *J. Path. & Bact.* **32**:247, 1929.

The distribution in the liver of an excess of iron, resulting from intravenous administration, was observed over a period of fourteen months, and the paths of the iron are described. The distribution and redistribution of iron in the organs are described. Iron held by the lungs is essentially a foreign substance and is transferred principally to the liver. It is suggested that the path of the iron in the lung is by way of the spleen. Iron is probably excreted by the cecum and the kidney, while part of the excess of iron in the liver is transferred to the lymphatic glands and remains in the body for some time.

AUTHOR'S SUMMARY.

EXPERIMENTAL ARTERIOSCLEROSIS. R. MANCKE, *Arch. f. exper. Path. u. Pharmakol.* **141**:228, 1929.

Mancke made a comparative study of the effects on the aorta of rabbits of certain aliphatic aldehydes, lactates, tartrates and irradiated ergosterol, with all of which Oswald Loeb had claimed it possible to cause arteriosclerosis in the rabbit. The work reported is essentially a repetition of Loeb's, but is based on a larger number of experiments. The compounds used and the daily dose per kilogram of body weight were formaldehyde bisulphide, 0.5 Gm.; acetaldehyde, 0.5 Gm.; sodium lactate, 0.6 Gm.; sodium pyruvate, 1 Gm. Ergosterol was administered in doses of from 1 to 50 mg. per animal per day, the duration of the administration being from two to nineteen days. In the case of the other compounds, the period of administration varied from two to as long as 202 days. The number of animals in each series in which arteriosclerosis was present at the end of the experiments was as follows: formaldehyde bisulphide, 11 of 24; acetaldehyde, 11 of 25; sodium lactate, 5 of 19; sodium pyruvate, 4 of 24; irradiated ergosterol, 16 of 26. With the aldehydes the degree of aortic involvement was greatest in from one to two weeks; after this period the animals appeared to become accustomed to the substances and the aortic lesions tended to heal. When irradiated ergosterol was used calcification and aneurysmal dilatation of the aorta were strikingly greater than after the other substances, and the degree of involvement was proportional to the duration of administration. In four dogs, each fed 9 Gm. of sodium lactate daily in a diet low in protein, over periods of from three to seven months, the results were negative, with the exception of one animal which revealed a slight degree of aortic change.

O. T. SCHULTZ.

EXPERIMENTAL RICKETS. T. SKAAR and K. HAEUPL, *Virchows Arch. f. path. Anat.* **271**:100, 1929.

Young dogs were fed on Mellanby's ricket diet. After three weeks the first signs of rickets appeared. The dogs were sick, awkward in their movements, ate

little, did not gain in weight. Roentgenograms of the radius and tibia showed poor ossification, thickening of epiphyses, widening of epiphyseal lines and frayed surfaces of the joints. Addition of 40 cc. of cod liver oil daily effected a rapid cure; the bone thickenings disappeared but the curvatures persisted. The phosphorus and calcium metabolism of the rachitic dogs was negative. The phosphorus and calcium content was low. After giving cod liver oil, the serum phosphorus rose quicker than the serum calcium. The bone of the cured animal contained less phosphorus and calcium than that of the control animal (which had 10 cc. of cod liver oil daily). In some dogs the phosphorus metabolism was more damaged, in others the calcium metabolism; there seem to be different forms of rickets. Large doses of phosphorus and calcium led to increase of phosphorus and calcium in the serum; but the bones of these dogs did not contain more phosphorus or calcium than those of the controls.

Nonlamellated bone was found in the controls also; it has nothing to do with rickets. Excessive formation of lime-free bone in the whole skeleton is characteristic of rickets. (N. Bocks method was used for demonstrating the lime-free bone.) The lime-free layers were ten times thicker than in the controls. Periosteal deposits of bone were less marked than in human rickets, but much more intense than in the controls. They are not of primary importance in the diagnosis of experimental rickets. Osteoblasts and osteoclasts did not differ from those in the controls and no such differences exist in human rickets. There were no signs of halisteresis. The bone-marrow of the rachitic dogs was fibrous: this is a secondary process due to irritation and stasis. The proliferating cartilage ("Knorpelwucherungszone") was from four to five times thicker than in the controls, occasionally from seven to ten times. The proliferating cartilage was vascularized from the marrow and from the perichondrium. The pathologic proliferations of the cartilage in the joint are secondary. It is the same with the formation of giant cells in hemorrhagic foci. The authors conclude that true rickets can be produced by deficient diet and cured by cod liver oil.

ALFRED PLAUT.

OXYGEN CONSUMPTION DURING MUSCULAR WORK IN HYPERTHYROIDISM AND IN HYPERTHYROID-LIKE STATES. H. HERXHEIMER, R. KOST and K. LANGE, *Ztschr. f. klin. Med.* **110**:1, 27 and 37, 1929.

The authors studied the consumption of oxygen during muscular work done by three groups of patients as compared with that of normal persons. Previous similar investigations on hyperthyroidism are criticized because of the paucity of observations made and because of the kind of work performed. The latter should be of a kind with which the subject is familiar and which requires no training to develop the necessary coordination. The work chosen in the present investigation was stair climbing done by each subject in slow, moderately rapid and rapid tempo. The Douglas bag method with gas analysis was used, samples of air being withdrawn for analysis immediately before and after the work done and at five minute intervals until a uniform level was reached. The increased consumption of oxygen due to work was compared with the recovery level rather than with the basal rate. The subjects studied, other than normal controls, were divided into three groups; eleven patients with instability of the sympathetic system or autonomic imbalance, with tachycardia and vasomotor instability, but with only slight subjective disturbance and with normal basal metabolic rate; a second group of twelve patients said to have exophthalmic goiter, with objective and subjective symptoms like those of hyperthyroidism but with no increase in basal metabolic rate, and eleven with hyperthyroidism accompanied by increased basal metabolic rate. In the first two groups the increased consumption of oxygen brought about by the work done was no greater than in the case of normal controls. The true cases of hyperthyroidism fell into three subgroups: in the first, there was no deviation in the consumption of oxygen as compared with normal; in the second, there was increased consumption and delay in recovery only when the work was done at rapid tempo; the third showed increased consumption of oxygen

and delayed recovery at all speeds of work. The last subgroup comprised persons with clinically the most severe forms of hyperthyroidism. The increased consumption of oxygen in the hyperthyroid group bore no relation to the degree of elevation of the basal metabolic rate.

O. T. SCHULTZ.

INSENSIBLE PERSPIRATION IN DECOMPENSATED CARDIAC DISEASE. E. ZAK, *Ztschr. f. klin. Med.* **110**:44, 1929.

Rubner first pointed out the importance in normal metabolism of the water lost by the body as insensible perspiration, and Benedict has recently made the determination of such loss practicable and has shown the amount of insensible perspiration to have a direct relation to the total energy metabolism, and within rather wide limits to be uninfluenced by clothing, temperature or air movement. Zak determined the insensible perspiration in three cases of decompensated cardiac disease, two of syphilitic aortitis with aortic regurgitation, and one of mitral stenosis with mitral and tricuspid insufficiency. In all, edema was constantly or intermittently present. In all, the water lost as insensible perspiration was greatly decreased. Even when the urinary output was increased above the water intake by digitalis or other therapy, the insensible perspiration still remained below normal. Increased oxygen intake with increased formation of water of oxidation within the tissues is not considered the true explanation of the interesting phenomenon noted. More probable but not yet proved the author considers a pathologically increased hydration of tissue colloids, the water being more firmly bound than normal, or increased intake of water from the atmosphere by the lungs and possibly also the skin, a condition which would interfere with the normal output of water from these sources.

O. T. SCHULTZ.

THE EFFECT OF ARSENIC ON THE MATURATION OF RED BLOOD CELLS. RAPHAEL ISAACS, *Folia haemat.* **37**:389, 1928.

The rate of growth and the factors influencing it, leading now to a precocious, now to a retarded maturation, is a problem which interests biologist and physician alike, for it involves cellular metabolism, that is, its growth and also probably the control of neoplastic tissues. For that purpose Isaacs used the erythrocyte which, he thinks, has certain advantages over other cells, in that it is easily available and recognizable; it has four distinct morphologic stages, and what is of great importance, the period of its maturation is short facilitating, thereby observations of changes at frequent intervals.

In previous studies the effect of hemorrhage, transfusion and roentgen irradiation on the maturation process has been investigated by the author. This work concerns itself with effects of arsenic on the maturation of the red blood corpuscles of the normal white mouse and also of some mice having tumors. Nontoxic and toxic doses of arsenic, acid and arsenious acid were used in the experiments. It was noted that nonlethal doses of arsenic caused a decrease in the percentage of both stages of young red blood cells, apparently as long as the arsenic was present in sufficient concentration in the body. After this, if no more arsenic was given there was a tendency for the more immature red blood cells to increase in percentage. In acute poisoning with arsenic, with death within twenty-four hours, there was no characteristic marked change in the absolute or relative number of young red blood cells.

In the tumor-bearing mice the depression in the number of young red blood cells was not so marked, but in these mice a study of the red blood cell formation showed that the bone-marrow did not have as much "reserve" as in the normal mice and that more cells were in the younger stages. The effect of arsenic acid is similar to that of arsenious acid in depressing the delivery of red blood cells from the bone-marrow, but the action is less intense and somewhat delayed.

Isaacs concludes that the arsenic solutions act as "depressors" of the bone-marrow with a decrease of production of young red blood cells. With the elimina-

tion of the arsenic the bone-marrow responds once more with an increase in the rate of maturation of the erythroblastic tissue and an increased production of young red blood cells.

B. M. FRIED.

THE LYMPHOCYTES IN NORMAL HUMAN BLOOD. AXEL WALLGREN, Arb. a. d. Pathol. Inst. d. Univ. Helsingfors 5:317, 1928.

The technical details must be studied in the original article. In addition to physical permeability a "physiologic permeability" is postulated and ascribed to a distinct mechanism under the control of the vital action of the cell.

### Pathologic Anatomy

THE RENAL LESIONS IN BRIGHT'S DISEASE. T. ADDIS, Am. J. M. Sc. 176: 617, 1928.

By a study of the urine, patients with chronic interstitial nephritis may be divided into three groups to which the names arteriosclerotic, degenerative and hemorrhagic chronic interstitial nephritis have been provisionally attached. In the seventy-five instances in which the urinary observations were compared with the renal lesion as it existed at the time of death, the arteriosclerotic group was characterized by an arteriosclerosis of the renal arteries and by a patchy fibrosis of the cortex; the degenerative cases showed granular, fatty or necrotic changes in the tubule cells, while the hemorrhagic group was distinguished by the presence of inflammatory lesions in the glomeruli. There is evidence to justify the belief that, clinically, bleeding means an active glomerular inflammation, an increase of epithelial cells in the urine means tubular degeneration, and a continuing slight excess over the normal of casts, protein and cells in the urine probably means a renal arteriosclerosis.

PEARL ZEEK.

RAYNAUD'S DISEASE ASSOCIATED WITH CANCER OF THE STOMACH. T. IZOD BENNETT and E. P. POULTON, Am. J. M. Sc. 176:654, 1928.

A case of Raynaud's disease with symmetrical gangrene of the fingers of both hands is reported. Postmortem examination revealed carcinoma of the stomach with metastasis to the inferior cervical ganglion. The presence of carcinoma cells in the ganglion was considered to be the cause of the Raynaud's disease. A similar case is quoted from the literature.

PEARL ZEEK.

SPONTANEOUS NONTUBERCULOUS PNEUMOTHORAX IN INFANCY AND CHILDHOOD. E. GORDON STOLOFF, Am. J. M. Sc. 176:657, 1928.

The common causes of spontaneous pneumothorax in order of frequency are tuberculosis, pneumonia, emphysema and gangrene. A review of the literature since 1844 reveals eighty-four cases of nontuberculous origin. Pathogenetically, pneumothorax may be caused by (a) degeneration of the lung (abscess, gangrene, bronchiectasis, infarction and empyema) or (b) rupture of the lung due to congenital defect, emphysema or foreign body. Three cases of postpneumonic pneumothorax (nontuberculous) are described. The diagnosis was made by roentgenography.

PEARL ZEEK.

ACCESSORY SPLEENS. MAURICE MORRISON, MAX LEDERER and W. Z. FRADKIN, Am. J. M. Sc. 176:672, 1928.

The failure of splenectomy to effect a permanent cure in essential thrombocytopenic purpura hemorrhagica may be caused by the presence of accessory



spleens which may undergo compensatory hypertrophy and gradually assume the pathic functions of the primary spleen. Four cases of thrombocytopenia are described, two with and two without accessory spleens.

PEARL ZEEK.

GASTRIC POLYPOSIS. ALFRED A. STRAUSS, JACOB MEYER and ARTHUR BLOOM, *Am. J. M. Sc.* **176**:681, 1928.

Two cases are added to the five previously reported in the literature. The differential diagnosis and treatment are discussed, and detailed microscopic and gross observations are given (with illustrations).

PEARL ZEEK.

A CASE OF EXTENSIVE BILATERAL PROGRESSIVE THROMBOSIS OF THE SMALLER BRANCHES OF THE PULMONARY ARTERIES. CHANNING FROTHINGHAM, *Am. J. Path.* **5**:11, 1929.

During life this patient clinically presented symptoms of unexplained shortness of breath and cyanosis on exertion gradually increasing over a period of months. The cause for it became apparent at autopsy as due to thrombosis of the smaller branches of the pulmonary arteries with resulting infarctions and injury to lung tissue. The thrombosis began in the smallest branches of the pulmonary arteries and propagated centripetally toward the larger branches. The cause for the beginning of the thrombosis or its tendency to propagate was not apparent. In the walls of some of the smallest branches of the pulmonary arteries were slight acute lesions for which the cause was not apparent. The relation of the tubercle-like lesions in the lung to the vascular lesions is unsettled.

AUTHOR'S SUMMARY.

A CASE OF MAMMARY GLAND TISSUE IN THE AXILLA. JOSEPH MCFARLAND, *Am. J. Path.* **5**:23, 1929.

The clinical history of the case, the surgical discovery of a collection of milk at the time of the operative removal of the tissue and the histologic observations all point clearly to this case as one of mammary tissue in the axilla in a woman, a unipara, 23 years of age.

AUTHOR'S SUMMARY.

THE INTIMAL LESION OF THE AORTA IN RHEUMATIC INFECTIONS. DAVID PERLA and MAX DEUTCH, *Am. J. Path.* **5**:45, 1929.

Two instances of macroscopic involvement of the aorta in recurrent rheumatic fever are described. A striking feature, which we believe has not been previously described, is the presence in one of the cases of an acute fibrinous lesion of the intima. In brief, the characteristics of the lesion are: Aschoff bodies in the adventitia; perivascular (in the acute stage, fanlike) infiltrations in the outer third of the media, with destruction of elastic tissue and muscle elements, and recent and organized fibrinous plaques in the intima, the connective tissue cells comprising the vascular organization tissue having a characteristic vertical orientation at the base of the intimal lesions.

AUTHORS' SUMMARY.

TISSUE CHANGES ASSOCIATED WITH VITAMIN "A" DEFICIENCY IN THE RAT. M. DAWSON TYSON and ARTHUR H. SMITH, *Am. J. Path.* **5**:57, 1929.

The principal changes associated with vitamin A deficiency in rats are a metaplasia of cuboidal or columnar epithelium in certain parts of the body, epithelial hyperplasia in various structures and infection. The metaplastic changes involve the following structures in order: the sublingual glands, the submaxillary glands, the epithelium of the renal pelvis and of the trachea and bronchi. The tongue is regularly involved before xerophthalmia appears. The serous type of sublingual gland is the first to be affected. The lesion in the tongue and submaxillary gland begins with a dilatation of the ducts and a metaplasia of the lining

epithelium accompanied by infection. In late cases the glandular tissue may be entirely destroyed by pressure from the dilated ducts and by necrosis due to infection. The submaxillary gland is not involved as constantly as the tongue. The epithelium of the renal pelvis may be involved fairly early. Metaplasia and infection are always present in the advanced cases. Renal calculi are prone to occur and when obstruction to the urinary outflow is present, pyonephrosis develops which is sometimes followed by perinephritic abscess. Epithelial metaplasia of the trachea and bronchi is not common. The most usual observation is an atrophy of the lining cells. Epithelial hyperplasia is striking in the tongue and renal pelvis. In the latter the hyperplasia overshadows the keratinizing process. Infection is always present even in the earliest stages and in late cases dominates the picture. No metaplastic activity has been seen without an accompanying infection, but infection has been observed in parts where metaplasia is absent. If the results of the dietary deficiency are not too severe, xerophthalmia clears rapidly with the administration of cod liver oil, and the weight curve rises abruptly. The extent of healing in the various organs depends largely on the amount of destruction due to infection which is present. Following the administration of cod liver oil abnormal epithelium and chronic or acute infection persist in the tongue and renal pelvis when the rat is apparently healthy.

AUTHORS' SUMMARY.

COMPENSATORY HYPERTROPHY OF THE THYROID. L. LOEB, *Am. J. Path.* **5**: 71 and 79, 1929.

Anterior pituitary substance, thyroid substance and thyroxin prevent compensatory hypertrophy of the thyroid in the guinea-pig and tend to produce changes in the thyroid that indicate a resting condition. The administration of potassium iodide does not prevent hypertrophy of the thyroid; on the contrary, the hypertrophy may be higher in animals receiving the iodide than in the control animals.

THE EFFECT OF UNDERFEEDING AND OF POTASSIUM IODIDE ON THE THYROID GLAND IN THE GUINEA PIG. JACOB RABINOVITCH, *Am. J. Path.* **5**:87 and 91, 1929.

Underfed guinea-pigs that have lost from 20 to 32 per cent of their weight show an entire absence of mitoses in the acinar epithelium of the thyroid gland, the colloid of which becomes solid and the acini small. The intraperitoneal injection of potassium iodide causes a rapid increase in the proliferation in the epithelium of the thyroid.

PRIMARY HYPERNEPHROMA OF THE LIVER. I. ABELL, *Ann. Surg.* **87**:829, 1928.

This is a report of a case of hypernephroma of the liver in a child 13 months of age, and a summary of ten cases collected from the literature.

N. ENZER.

BENIGN TUMORS OF THE STOMACH. J. T. MASON and M. F. DWYER, *Ann. Surg.* **88**:866, 1928.

Three cases are reported of leiomyoma, polyp and fibromyoma of the stomach. None of these cases gave any symptoms, and the lesion was demonstrated by the roentgen ray. In one case the condition had been diagnosed as spindle cell sarcoma, but after seven years the patient was still alive and the pathologist reclassified the case as a leiomyoma.

N. ENZER.

PRIMARY EXTRA-RENAL HYPERNEPHROMA. A. E. BOTHE, *Ann. Surg.* **89**:1028, 1928.

The author reports a case of a tumor in the region of the right suprarenal gland with metastases in the liver, but not involving either the kidney or the suprarenal gland. The tumor had the histologic structure of hypernephroma.

N. ENZER.

FOCAL NECROSIS OF THE LIVER. J. W. EDINGTON, J. Path. & Bact. **32:1**, 1929.

The primary lesion in focal necrosis of the liver in infection with *B. aertrycke* is death of liver cells; the infiltration with macrophages is secondary. Bile stasis is an important factor in localizing the lesions.

AUTHOR'S SUMMARY.

CHRONIC PEPTIC ULCER OF THE OESOPHAGUS. M. J. STEWART and S. J. HARTFALL, J. Path. & Bact. **32:9**, 1929.

A case of chronic peptic ulcer of the lower end of the esophagus is reported. The chief symptoms were high epigastric pain of five months' duration and recurrent hematemesis for a fortnight; dysphagia was not a prominent symptom. Death was due to perforation of the ulcer into the right pleural sac. An interesting feature of the case was the presence in the upper part of the esophagus of two large patches of heterotopic gastric mucous membrane of fundal type; the possible relationship of this developmental abnormality to chronic peptic ulceration of the esophagus is discussed.

AUTHORS' SUMMARY.

RETROPERITONEAL GANGLIONIC NEUROMA. D. F. CAPPELL, J. Path. & Bact. **32:43**, 1929.

A case is recorded of an unusually large ganglionic neuroma which presents throughout a uniform structure of adult ganglionic cells and nerve fibers. The majority of the fibers are of nonmedullated type and the remarkable feature is their enormous number. They possess a well formed sheath of Schwann and an outer connective tissue sheath of Henle. Two varieties of axis cylinder processes have been recognized; coarse relatively uniform fibers, and fine fibers with the varicosities of sympathetic type. The interstitial tissue is unusually myxomatous, but no neuroglial elements other than the neurilemma cells have been recognized. No trace of rosetts or other neuroblastic elements has been found, and the subsequent history of the case confirms the view that the tumor is of simple type.

AUTHOR'S SUMMARY.

THE NERVOUS SYSTEM IN RATS FED ON DIETS DEFICIENT IN VITAMINS B<sub>1</sub> AND B<sub>2</sub>. RUBY O. STERN and G. MARSHALL FINDLAY, J. Path. & Bact. **32:63**, 1929.

Rats fed on a diet deficient in both vitamin B<sub>1</sub> and B<sub>2</sub> exhibit only slight chromatolytic changes in the ganglion cells of the cord. Rats fed on a diet deficient in vitamin B<sub>1</sub> exhibit the same changes but to a greater extent for the same duration of life. In addition, when symptoms of paralysis are of long standing, early degeneration may be found in the myelin of the peripheral nerves. The histologic changes found in the nervous system of rats fed on a diet lacking vitamin B<sub>2</sub> consist in swelling and vacuolation of the anterior horn cells of the spinal cord with the deposition in them of lipochrome pigment, a noticeable increase in the surrounding satellite cells and an increase in the number of granules in the peripheral nerves.

AUTHORS' SUMMARY.

A CASE OF DIABETES MELLITUS WITH ACROMEGALY AND LIPAEMIA. JOHN GRAY, J. Path. & Bact. **32:71**, 1929.

In a patient dying from diabetic coma and presenting also certain features of acromegaly, the following lesions were noted post mortem: lipemia, consequent mononuclear hyperplasia in the spleen, pancreatic, hepatic and renal cirrhosis, cholelithiasis, chromophobe adenoma of the pituitary gland, gastric catarrh with multiple gastric ulcers and hemorrhage into the stomach.

AUTHOR'S SUMMARY.

DIFFUSE AND NODULAR FIBROSIS OF ADVENTITIA OF AORTA. W. G. BARNARD, *J. Path. & Bact.* **32**:95, 1929.

A widespread fibrosis of the adventitia of the aorta is described; the suggestion is made that it is due to rheumatism.

AUTHOR'S SUMMARY.

SIDEROSIS OF THE GLOBUS PALLIDUS: ITS RELATION TO BILATERAL NECROSIS. Goeffrey HADFIELD, *J. Path. & Bact.* **32**:135, 1929.

The walls of the blood vessels of the healthy globus pallidus are often infiltrated with iron salts which are derived from the nucleus itself. It is likely that the process is one of evolutionary atrophy. It predisposes to the acute bilateral destruction of these nuclei which is frequent in coal-gas poisoning.

AUTHOR'S SUMMARY.

CONGENITAL VALVES, PSEUDOVALVES AND STENOSIS OF THE PYLORUS AND DUODENUM. A. COSTA, *Arch. di pat. e clin. med.* **7**:501, 1928.

At the autopsy of a woman, aged 60, a valvelike formation was found in the pyloric canal; the basal attachment of this pyloric valve measured 2 cm. in width, 1 cm. in length and 3 mm. in thickness. In its close vicinity, there was another but smaller, tongue-like, mucous projection. Microscopically, it showed the structure of a normal mucosa (transition between pyloric and duodenal type) and contained a few smooth muscle cells, which were branching from the muscularis mucosae. The author classified this valvular formation of the pylorus, which was observed only once in about 20,000 autopsies, as a developmental disturbance and as an excess in growth. The literature contains only one paper dealing with this subject, published by Arregger in 1896. These congenital valves of the pylorus should not be confused with pseudovalvular formations, which are the result of a benign neoplasm, as described by Magnus-Asleben, and originate from a proliferation of glandular and muscular tissues (adenomyoma of the pylorus). The author then describes a typical case of a pyloric pseudovalve due to traction, microscopically an adenoma, in a man 67 years of age. Various forms of congenital pyloric stenosis are discussed in detail and, in accordance with Chiari, three types are introduced: (a) congenital stenosis of mucous type (stenosis of Landerer-Maier type); (b) congenital stenosis of muscular type (hypertrophic stenosis, stenosis of Hirschsprung type), and (c) congenital stenosis of combined type (a variety of Landerer-Maier type). The theories regarding the development of congenital stenosis of the duodenum and of the duodenal atresia are exhaustively presented. The studies of Schridde, Beneke and Tandler, which tend to prove an embryonal epithelial occlusion of the duodenum, are contrasted with the theories propagated by Marchand, Thorel and Fanconi, who assume the existence of a fetal enteritis.

E. L. MILOSLAVICH.

THE RETICULAR TISSUE IN AMYLOID DEGENERATION. L. LA GRUTTA, *Sperimentale: Arch. di biol.* **82**:381, 1928.

The changes in the reticulum in organs of man or in the organs of animals, in which amyloid degeneration is not far advanced, are increase of volume, varicosity, disintegration and resistance to impregnation of the fibrils by silver. The appearances suggest that the reticulum is concerned in the early formation of amyloid.

FUNGI IN GASTRIC ULCERS. O. BARTOLI, *Sperimentale: Arch. di biol.* **82**:421, 1928.

Fungi are frequently found in gastric ulcers, not only in the superficial layers and necrotic areas, but also in the deeper parts. The fungi, while perhaps not the cause of the ulcer, may be important factors in its maintenance and in changing an acute into a chronic ulcer.

MEDIAN CERVICAL CYST AND FISTULA. A. MAGLIULO, *Sperimentale: Arch. di biol.* **82**:455, 1928.

The most frequent congenital median malformation of the neck is thyroglossal cyst, arising from remnants of the thyroglossal duct. Median cervical cysts may arise also from displaced thyroidal tissue. These cysts may result in median fistula.

PRIMARY, GENERALIZED ROUND CELL SARCOMA OF THE LYMPH GLANDS. E. HERZOG, *Centralbl. f. allg. Pathol. u. path. Anat.* **44**:129, 1928.

A girl, aged 15, entered the hospital because of painless, generalized enlargement of the lymph glands of five weeks' duration. Two weeks later a small tumor developed beneath the skin of the right third intercostal space, and eight days later an abscess of the palate. The lymph glands were the size of a plum; the Wassermann reaction of the blood was negative, and the blood picture was typical of a secondary anemia. A clinical diagnosis was made of aleukemic leukemia. At autopsy there was a tumor-like systemic involvement of all lymph glands, and there were small metastases in the pericardium, trachea, sternum, skin of the right shoulder and marrow of the femur. Microscopically, the structure of the lymph glands was distorted by many large round or polygonal cells with abundant protoplasm with large vesicular nuclei rich in chromatin and with abundant mitoses. The capsules of the lymph glands generally were thickened but free from infiltrations of tumor cells or small lymphocytes, whereas in the region of the mediastinum and trachea the invasive character of the tumor was evident. The origin of this large round cell sarcoma of the lymph glands was therefore thought probable in the mediastinum.

GEORGE RUKSTINAT.

DIFFUSE ACUTE INTERSTITIAL ADENOHYPOPHYSITIS. W. BERBLINGER, *Centralbl. f. allg. Pathol. u. path. Anat.* **44**:161, 1928.

In a woman, aged 34, who was eight months' pregnant, with a blood pressure of 180 systolic and 140 diastolic, scanty urine containing 20 per cent albumin and a premature separation of the placenta necessitating delivery, death occurred from uremia. The hypophysis weighed 0.86 Gm. and its posterior lobe was normal. In the anterior lobe, particularly in its dorsal portion, there were infiltrations of lymphocytes and lymphoblasts, and rarely leukocytes about the alveoli and along the capillaries. The capillary endothelium was unchanged. The alterations herein noted were found lacking in the hypophyses of five other women dying of eclampsia.

GEORGE RUKSTINAT.

THE HARDNESS OF GLANDULAR ORGANS AND THE CHANGES AFTER DEATH. HANS MELTZER, *Klin. Wchnschr.* **7**:2477, 1928.

Sclerometric measurements of the liver, spleen and kidney in a variety of warm-blooded animals were made at and following death for several days. There is a definite increase in the hardness of these tissues (regularly of the liver and kidney, not without exception of the spleen) which reaches its maximum from three to eight hours after death. This change, in theoretical discussion, is ascribed to a postmortem alteration of the protein colloid of the cells.

AUTHOR'S SUMMARY.

SUPPURATION OF THE THORACIC DUCT. E. KRYLOFF, *Virchows Arch. f. path. Anat.* **266**:1, 1927.

An instance of this rare condition is described, which occurred during an attack of grip.

B. R. LOVETT.

THE EFFECT OF STRETCHING ON SKELETAL MUSCLE. A. STAUSS, Virchows Arch. f. path. Anat. **266**:4, 1927.

During pregnancy, destruction and new formation of muscle fibers in the embryonic manner were observed. In cases of infection, especially acute, more varied and marked degenerative changes were found. During great increase in the intra-abdominal pressure, tearing and scar formation occurred. Proliferation of nuclei at the ends of the fibers indicated an appositional growth of the stretched abdominal muscle, which should be a suitable object for investigations of the growth and hyperplasia of the musculature in general.

B. R. LOVETT.

BONE FORMATION IN THE WALL OF THE HEART. H. EDELMANN, Virchows Arch. f. path. Anat. **266**:51, 1927.

Twenty-three instances of bone formation in the heart muscle have been described in the literature, only one of which was in man. In this case a piece of long bone with a cartilaginous epiphysis was found in the left auricular wall of a guinea-pig. The author explains the development of this anomaly according to the blastomere theory of Marchand and Bonnet, rather than as a metaplastic growth.

B. R. LOVETT.

CONSEQUENCES OF LIGATION OF THE HEPATIC ARTERY. L. LOEFFLER, Virchows Arch. f. path. Anat. **266**:55, 1927.

Loeffler studied the effects of ligation of the hepatic artery in sixty rabbits. General changes of a mild nature occurred in the portal areas: widening of the lymph vessels, the branches of the portal vein and the bile ducts, and later increase in collagenic fibers without cell increase, and decrease in elastic and muscle tissue in the vessel walls. He attributed these changes, not directly to deprivation of blood supply, but to paralysis of the vessel walls, since nervous tissue is the first to suffer from anemia. In the lobules of the liver themselves, partially deprived of blood supply, hyperemia occurred: widening of the capillaries with slowing of the blood flow, and shrinking of the liver cells. Nerve injury was regarded as the basis for this change also.

Localized changes, less constant but of more marked degree, were also found. Necrosis of the gallbladder was almost constant, followed by leakage of bile into the parenchyma immediately around it, so that it too became necrotic. Scattered sections of the larger bile ducts underwent necrosis in from thirty to 120 minutes. Paralysis and dilatation of the walls took place, allowing them to become permeated with bile, which acts as a strong chemical irritant to the nervous mechanism. This change in the ducts was sometimes accompanied by extensive stasis and necrosis in the neighboring lobules, also attributed to the irritant effect of the bile. The larger necrotic places became surrounded by a zone of fibrous tissue, with hypertrophied bile ducts and atrophied parenchyma.

Ligation of the hepatic artery was shown to act, therefore, not directly, but through the irritant effect of the bile set free into the tissue. The change reached its height during the first few days, and thereafter was regressive. The liver ceased to function in glycogen and fat metabolism for a time. Deaths were in proportion to the number and extent of the necrotic places.

B. R. LOVETT.

THE EFFECT OF ACID AND ALKALINE FEEDINGS PRODUCING AMYLOID IN MICE. R. RABL, Virchows Arch. f. path. Anat. **266**:133, 1927.

In mice fed on a diet rich in cholesterol, and either acid or alternating acid and alkaline in reaction, the presence of amyloid could be shown in a number of organs. It was most frequent in the spleen and liver, less so in the duodenum, kidneys and pancreas. Skin infections could not be ruled out in all cases. These feedings were also frequently accompanied by waxy degeneration in the heart and body musculature, and calcification of the arteries. Mice fed on alkaline

foods tended to develop anemia, but rarely showed amyloid or waxy degenerations. In the production of this form of degeneration, therefore, acid foods and those rich in cholesterol seem to be of significance.

B. R. LOVETT.

CHANGES IN THE SKELETAL MUSCULATURE IN TRICHINOSIS. H. NEVINNY, Virchows Arch. f. path. Anat. **266**:185, 1927.

Five cases of trichinosis in man and eighteen experimental infections in animals were studied. Gross anatomic changes in the muscles were found in only two animals and in none of the cases in man. The presence of glycogen in *Trichinellae* could be easily demonstrated, while the surrounding muscle was poor in this substance. The fibrillar substance showed degeneration, with fine, basophilic granulation, besides waxy and hydropic degeneration, and simple atrophy. Fatty change was marked in three cases in human beings, but was insignificant in the animals. Two stages in encapsulation were distinguishable. First, the coiled worms were seen to be surrounded by a substance made up of the basophilic, granular contents of the fibers. In the chronic stage, permanent hyaline capsules were formed. This process was explained as an antigen-antibody reaction. Foreign body giant cells, of mesenchymal origin, were observed near the dying *Trichinellae*. Clinically observed painfulness corresponded to the degree of exudate and cellular infiltration in the muscles. This inflammatory reaction was more marked in man than in the animals. Nonencapsulated worms rapidly underwent destruction, in which process collections of white blood cells and tissue cells played a part. Destruction with liberation of the substance of *Trichinellae* was especially prominent in man, accounting for the severe general symptoms of the disease. The observations indicated that man reacts more strongly to *Trichinellae* than do guinea-pigs or rabbits, while rats readily succumb to acute intestinal trichinosis.

B. R. LOVETT.

A RARE MALFORMATION OF THE TRICUSPID VALVE. A. ARNSTEIN, Virchows Arch. f. path. Anat. **266**:247, 1927.

A case of congenital malformation of the tricuspid valve (Ebstein's disease) is described. There was dilatation of the right auricle, contraction of the right ventricle with poor development of its wall, and open foramen ovale. Clinically, systolic and diastolic murmurs, thrills, cyanosis and polycythemia were observed.

B. R. LOVETT.

HISTOLOGIC FINDINGS IN THE RETICULO-ENDOTHELIAL SYSTEM IN DIFFERENT FORMS OF PUERPERAL FEVER. H. E. SCHEYER, Virchows Arch. f. path. Anat. **266**:255, 1927.

The course of puerperal fever is influenced, aside from the virulence of the organism, by the resistance of the body, especially the reactivity of the reticulo-endothelial system. Three types of the latter have been described: lack of reaction, good reaction and reaction at first satisfactory but becoming exhausted. In patients with different forms of puerperal fever, lack of reaction was found in those dying of foudroyant sepsis and rapidly fatal peritonitis. Reaction at first active, but becoming exhausted, was correlated with thrombophlebitis ending fatally after a prolonged course. In patients who recovered, satisfactory reaction of the reticulo-endothelial system could be assumed in the absence of occasion for histologic examination.

B. R. LOVETT.

LYMPHOSTASIS. W. TALALAIEV, Virchows Arch. f. path. Anat. **266**:268, 1927.

Following interruption of lymph flow, growth of the epithelium and stroma occludes the lumen of the vessel. In the nodes, the adenoid tissue disappears first, the reaction centers remain somewhat longer, the sinuses are converted into a network of lymph capillaries and the stroma becomes collagenous.

B. R. LOVETT.

EPITHELIAL METAPLASIA IN THE LUNGS. P. GUNKEL, *Virchows Arch. f. path. Anat.* **266**:310, 1927.

An instance of metaplasia on the basis of a chronic inflammation is described, in which cylindric and pavement epithelia were observed in the alveoli of the lungs.

B. R. LOVETT.

A LYMPHO-EPITHELIAL TUMOR OF THE THYROID. A. BABES, *Virchows Arch. f. path. Anat.* **266**:320, 1927.

A benign tumor of the thyroid is described, probably originating from thymus tissue. It consisted of lobules of lymphoid cells, containing islands and strands of epithelium.

B. R. LOVETT.

CHANGES IN THE THYROID GLAND IN AVITAMINOSIS B. S. A. SATWORNITZKAJA and W. S. SIMNITZKY, *Virchows Arch. f. path. Anat.* **266**:329, 1927.

In the thyroids of rats on a diet lacking in vitamin B, there was found at first increased secretory activity, with hypertrophy and new growth of follicles and increase in colloid. Later, rupture of several follicles occurred, with escape of colloid, along with necrobiosis of the follicle cells. Since no repair took place, this process was followed by decrease in the size of the gland. In the end-stage, signs of exhaustion and decreased function became evident, but not to any marked degree.

In the thyroids of pigeons the same changes were observed, except that evidence of terminal decrease in function was lacking. Necrobiotic changes in the single cells appeared to be the result of increased activity with disturbance in nutrition, in consequence of the vitamin lack. These changes were too slight, however, to account for a decrease in function.

The results present no evidence of significant decrease in secretion during vitamin B inadequacy, but, on the contrary, show an increase, for a certain length of time in rats, and until the end in pigeons.

B. R. LOVETT.

HERMAPHRODITISM. G. SCHAPIRO, *Virchows Arch. f. path. Anat.* **266**:392, 1927.

A hermaphrodite is described whose secondary sexual characters partook of both masculine and feminine types. One of the internal sex organs was an immature ovary, and the other a mixture of ovary and testis. Removal of these organs and implantation of animal testes failed to change the patient in any way. The author discusses classifications of hermaphroditism, and finds a difference in degree only between the true and pseudo types.

B. R. LOVETT.

DISPLACEMENT OF THE POSTERIOR LOBE OF THE HYPOPHYSIS. A. PRIESEL, *Virchows Arch. f. path. Anat.* **266**:407, 1927.

Priesel observed several instances in which the posterior lobe of the hypophysis lay outside the sella on the base of the brain. It was connected with the anterior lobe by a thin strand of tissue. Three types of displacement have been found. There was no functional significance associated with this anomaly.

B. R. LOVETT.

SYMPATHETIC TUMOR OF THE SUPRARENAL GLAND. F. MATZDORFF, *Virchows Arch. f. path. Anat.* **266**:416, 1927.

A tumor of the suprarenal gland was examined at autopsy, consisting of cells of sympathetic nervous system origin. The liver tissue was almost entirely replaced by cells of the same type. This was thought to be a primary disease of the liver rather than a metastatic growth.

B. R. LOVETT.



THE APOCRINAL SWEAT GLANDS. H. HERZENBERG, *Virchows Arch. f. path. Anat.* **266**:422, 1927.

An investigation was made on 200 cadavers of men, women and children of these large sweat glands, found chiefly in the axillary and genital regions, and secreting a substance of characteristic odor. The full number of glands was found at birth, but actively could not be distinguished before sexual maturity. The number appeared to be somewhat greater in boys than in girls. In adults, the glands were equally widespread in the two sexes, and were functional from puberty throughout the rest of life, with some variations. Thus, in wasting disease and in old age their activity decreased along with that of other organs. In women, there was hypertrophy and hypersecretion during menstruation and pregnancy, and moderation of activity without complete cessation after the menopause. The glands appeared to function not only as "accessory sex glands," but also as organs for determining the characteristic odor through most of life, independently of the other sex organs.

B. R. LOVETT.

HISTOGENESIS OF RENAL TUBERCLES. CLAUSSEN, *Virchows Arch. f. path. Anat.* **266**:456, 1927.

The first changes in miliary renal tuberculosis of pigs and cows were localized in the interstitial tissue of the cortex, in the form of small collections of epithelioid and round cells. Primary disease of the glomeruli, as occurs in experimental infections, was never found. The cells making up the tubercle were derived from the histiocytes of the interstitial tissue and the endothelial cells of the capillaries, never from the renal epithelium. Fully developed tubercles showed the usual epithelioid and lymphoid zones, and later gave evidence of degeneration in the form of fatty change and finally caseation.

B. R. LOVETT.

TUBERCULOSIS OF THE SEROUS MEMBRANES. E. RANDEATH, *Virchows Arch. f. path. Anat.* **266**:475, 1927.

This histologic study of tuberculosis of serous membranes from autopsy material revealed the two forms, miliary tuberculosis without exudate and tuberculous inflammation with exudation, but the transition between the two was found to be gradual. The development of the exudate could be traced through various stages, beginning with injury to the surface epithelium, followed by circulatory disturbance and exudation. The exudate in this stage varied in composition and in the predominant cell type, and was not of a specific character except as it contained bacilli. The growth of granulation tissue followed rapidly, with the formation of characteristic tubercles, the first specific change. Caseation was observed in some of the cases, both in the granulation tissue and in the exudate, with masses of bacilli, and involving all the cells present in the region. Granulation tissue could sometimes be found growing into the caseous masses. In the end-stage, there was conversion of the organized exudate into solid, nonspecific scar tissue.

B. R. LOVETT.

TUBERCULOSIS OF THE PAROTID GLAND. L. HASLHOFER, *Virchows Arch. f. path. Anat.* **266**:499, 1927.

A case of isolated tuberculosis of the parotid gland is described, of the nodular caseous type, with miliary and conglomerate tubercles. The mode of infection is discussed, and of the various possibilities, infection through the blood or lymph stream is held to be the most probable.

B. R. LOVETT.

"YELLOW (CHROMAFFIN)" CELLS IN THE GASTRO-INTESTINAL TRACT. H. HAMPERL, *Virchows Arch. f. path. Anat.* **266**:509, 1927.

The yellow cells are one of the types found in the intestinal epithelium of man and most vertebrates. They can be distinguished by the staining reaction with

silver salts, which color the nuclei and granules black without the addition of reducing substances. This reaction distinguishes them from the chromaffin cells of the suprarenal gland, which they resemble somewhat. The granules are situated at the base of the cells, below the round nucleus. The yellow cells probably originate from undifferentiated cells of the intestinal epithelium, and have an excretory function about which little is known.

In the stomach, Hamperl found these cells in the islands of intestinal mucosa which appear there in the various conditions commonly known as "chronic gastritis." Yellow cells were absent or few in number in normal gastric mucous membrane, but were frequent in "chronic gastritis," with or without carcinoma. He regards them as the result of faulty cell differentiation in the course of regeneration of the epithelium. Yellow cells were found predominating in carcinoid tumors, but were numerous in only three of fifty-one other carcinomas of the gastro-intestinal tract, one in the cecum, one in the rectum and one in the stomach. Hamperl does not believe in a fundamental distinction between carcinoids and other intestinal carcinomas.

B. R. LOVETT.

THE ETIOLOGY OF GASTRIC AND DUODENAL ULCERS. I. HONDA, *Virchows Arch. f. path. Anat.* **266**:549, 1927.

Injections of lycopodium into the gastric and duodenal veins of dogs did not produce ulcers, but injection into the arteries was followed by the development of ulcers in more than 100 dogs. In the stomach, the location, most frequently at the pylorus and lesser curvature (regions poor in arterial anastomoses), and the form, round with steplike margins, resembled the round ulcer in man. The lycopodium produced thrombosis, chiefly in the arteries of the submucosa, followed by anemic necrosis of the epithelium, and digestion by the gastric juice. Thus, arterial circulatory disturbance appeared to be the cause of the ulcer. Erosions also were sometimes produced, but these healed promptly, and bore no relation to the ulcers. The latter healed within one month. For production of a chronic lesion, some other disturbing factor was needed, such as passive congestion through ligation of the gastric veins, removal of the celiac ganglion and plexus, or injection of *Staphylococcus aureus*. In the chronic ulcers, the characteristic form, as well as evidence of arterial thrombosis, became indistinct in the course of time. This fact makes it understandable that organic changes in the arteries of the region of the ulcer become difficult to recognize. Results were similar following injections into the duodenal arteries.

A study of autopsies on man revealed: ulcers present in 4.79 per cent, the most frequent age being the fourth decade, men affected oftener than women, and circulatory disturbance, atherosclerosis, arteritis obliterans and thrombosis frequent accompaniments. Honda believes that ulcers arise on the basis of organic change in the gastric arteries with digestion of the mucous membrane by gastric juice. The chronicity depends on factors influencing reparative activity, passive congestion, nervous disturbance and infection.

B. R. LOVETT.

ENDARTERITIS OBLITERANS. H. GOECKE, *Virchows Arch. f. path. Anat.* **266**:609, 1928.

Necropsy of a patient who died from endarteritis obliterans revealed changes in the medium-sized arteries of the extremities, consisting of growth of the intima and consequent narrowing or obliteration of the lumen. No evidence of a primary arteriosclerosis or thrombosis was found. The intimal growth was attributed to repeated spasm with subsequent dilatation of the vasa vasorum supplying the medium-sized arteries, leading to increased permeation of the vessel wall by fluid. Gangrene was attributed to alternating spasm and dilatation in the capillary region, along with slowing of the blood stream, so that a slight trauma was followed by complete stasis and necrosis. As etiologic factors, the action of nicotine, alcohol, cold and other injurious agents on constitutionally inferior nerves of the vascular system is suggested.

B. R. LOVETT.

THE STRUCTURE AND PHYSIOLOGIC CHANGES OF THE CEREBRAL ARTERIES. W. M. HACKEL, *Virchows Arch. f. path. Anat.* **266**:630, 1928.

Hackel points out the importance of recognizing the normal histologic structure and the changes due to the age of the cerebral arteries. His studies showed the chief characteristics of these arteries to be the thick lamina elastica interna, absent lamina elastica externa and poorly developed adventitia. Splitting of the lamina elastica interna was observed, beginning in childhood in the largest arteries, and spreading to the smaller vessels during later life. He concluded that hyperplasia of the elastic tissue of the intima, of greater or less degree, is a normal physiologic change of advancing age.

B. R. LOVETT.

THE SIGNIFICANCE OF THE VENAE MINIMAE THEBESII FOR THE BLOOD DISTRIBUTION TO THE HEART MUSCLE. J. KRETZ, *Virchows Arch. f. path. Anat.* **266**:647, 1928.

Kretz reached the following conclusions from perfusion experiments carried out on the hearts of cadavers: The Thebesian vessels are an important part of the coronary system. They are found in all sections of the heart, and are especially well developed in the interventricular septum and at the apex. They provide a direct connection between the coronary vessels and the chambers of the heart. Conditions for blood flow through the Thebesian vessels are most favorable during systole, while the coronary vessels carry most blood during diastole. The presence of the Thebesian vessels and the consequent possibility of nourishing the heart from its own chambers explain the frequent lack of correlation between disease changes in the coronary arteries and the function of the myocardium. In spite of high grade narrowing of the coronaries, the heart can still be capable of full work. A further possibility of nutrition lies in absorption of substances from the blood directly through the endocardium.

B. R. LOVETT.

RETICULOCYTES IN EMBRYOS AND THE NEW-BORN. R. JÜRGENS, *Virchows Arch. f. path. Anat.* **266**:676, 1928.

The blood of 300 mouse embryos was investigated. Two developmental series of red cells could be distinguished, the megaloblastic and the normoblastic. In young embryos, all erythroblastic cells contained vitally stained granulations, and a definite formation and growth of substantia granulofilamentosa could be determined, similar for both series. In later embryonic life, the number of reticulocytes diminished progressively with the disappearance of the cell nuclei until birth. New-born mice had an average of from 60 to 70 per cent of reticulocytes, falling to from 30 to 40 per cent in the first hours of life, and to from 0.5 to 2 per cent after a few weeks. In human infants the percentage was 7 at birth, 2 at 10 days and 0.7 at 6 weeks. In premature infants, the number was much greater, from 11 to 30 per cent at birth. The substantia granulofilamentosa represents a constant morphologic stage in the process of normal development of all hemoglobin containing blood cells in man and in animals. This substance is a remainder of the original blood cell protoplasm, and diminishes as pyknosis and karyolysis of the nucleus occur, until it disappears entirely in the mature cell.

B. R. LOVETT.

SIGNIFICANCE OF LIPOIDSIDEROSIS OF THE CEREBRAL CAPILLARIES FOR HYPERTONIA AND ARTERIOSCLEROSIS. M. MÜHLMANN, *Virchows Arch. f. path. Anat.* **266**:712, 1928.

The author states that essential hypertension is due to an obstruction to the circulation, the cause of which is unknown, but is generally assumed to be of a nervous nature. Physiologic hypertension with advancing age follows from the comparative narrowing of the arteries in comparison with the size of the heart. Pathologic hypertension is distinguished chiefly by its effect on the brain. The cerebral arteries are characterized by the presence of lipid granules in the endo-

thelium, with increasing blood pressure. The course of these iron-containing granules is the red blood cells which are driven into the wall under the influence of high pressure, and are phagocytosed. From there they may be carried to the nerve cells; lipoidsiderosis of the brain. As a consequence of the narrowing of the arteries, with hypertension and oxygen insufficiency, the process becomes itself a cause of further hypertension, and is the beginning of arteriosclerosis. Pathologic hypertonia is then the result of the action of injurious agents (infection, intoxication) on the physiologic hypertension, which is due, first, to conditions of growth, and, second, to lipoidsiderosis of the cerebral capillaries. Arteriosclerosis is the end-result of hypertension.

B. R. LOVETT.

CEREBRAL CHANGES IN HUMAN TRICHINOSIS. E. GAMPER and G. B. GRUBER, *Virchows Arch. f. path. Anat.* **266**:731, 1928.

Although cerebral symptoms have long been known to occur in severe cases of trichinosis, there has been little investigation of the pathologic changes. The authors examined the brain of a person who died in the fifth week of an acute trichinosis, and found edema and infiltration of the markedly hyperemic meninges, along with regressive and progressive changes in the brain. The latter consisted of nodules of glia cells, in some of which *Trichinae* could be demonstrated. The regressive changes observed were scattered necrotic foci, sometimes accompanied by embolism or thrombosis of the vessels, fatty degeneration and growth of glia fibers. It seems justifiable, therefore, to speak of encephalitis in trichinosis.

B. R. LOVETT.

SPLenic INFARCTS IN TYPHOID FEVER. S. BÉZI, *Virchows Arch. f. path. Anat.* **266**:748, 1928.

The circumscribed necroses in the spleen occurring in typhoid fever are infarcts, caused by necrosis and tearing of the lamella elastica interna and consequent thrombosis of the artery. Necrosis of the elastic tissue is due to the toxin of the typhoid bacilli. These infarcts are specific for typhoid infection, and can be distinguished from those arising from embolism. In more than 500 cases, 4.15 per cent showed infarcts arising from tearing of the elastic tissue, occurring most frequently during the fourth week. Suppuration of the infarcts is usually due to the typhoid bacillus itself. There is no relation between central necrosis of the mesenteric lymph nodes and the frequency of splenic infarcts.

B. R. LOVETT.

THE LIVER IN AFRICAN YELLOW FEVER. W. H. HOFFMANN, *Virchows Arch. f. path. Anat.* **266**:769, 1928.

Histologic examinations were made of the livers from a number of cases of suspected yellow fever in West Africa, and in all the presence of this disease could be demonstrated. The chief characteristic was the simultaneous presence of numerous cells which had undergone fatty degeneration and completely necrotic cells, mixed together. Near the central vein and at the periphery were a few well preserved cells, but the picture was never one of a purely central or peripheral necrosis. These constant changes were attributed to the toxin of *Leptospira icteroides*. The African cases showed full agreement with those in the American epidemics. Similar changes are found only in acute yellow atrophy and in a few intoxications, never in acute infectious diseases. Histologic examination of the liver is the simplest and most reliable method for showing the presence of yellow fever, and hence is of the greatest value in the prevention and checking of epidemics.

B. R. LOVETT.

THE ETIOLOGY OF MALACOPLAKIA OF THE BLADDER. Z. KAIRIS, *Virchows Arch. f. path. Anat.* **266**:788, 1928.

A case of malacoplakia of the urinary bladder is described in a girl, aged 1½ years, with an infected double kidney on one side. This disease is usually found

in older persons. Cystoscopic examination shows the mucous membrane studded with yellow-white, raised plaques, with a depression in the center, and sometimes ulceration in the later stages. Histologically, the plaques are made up of lymphocytes and large round or angular cells, with small round nuclei, corresponding to fibroblasts, which are characteristic for the condition. There may also be iron-containing inclusion bodies. The condition has been variously regarded as a granuloma, the result of nonspecific infection, or of long-standing cystitis. The latter seemed to be the causative factor in this case.

B. R. LOVETT.

**LIPOMA OF THE ADIPOSUM PARARENAL.** L. JAFFÉ, *Virchows Arch. f. path. Anat.* **266:801**, 1928.

Jaffé reports a case of lipofibrosarcoma, with necropsy observations, in which the tumor weighed 11.3 Kg. The condition originated in the body of fat behind and lateral to the kidneys. The tumor was bilateral, retroperitoneal on one side and intraperitoneal on the other. He found nine instances in the literature of tumors with a similar origin, some pure lipomas and some mixed with fibrous or myxomatous tissue.

B. R. LOVETT.

**COMPLETE RUPTURE OF THE RIGHT BRONCHUS.** S. I. KRINITZKI, *Virchows Arch. f. path. Anat.* **266:815**, 1928.

A girl, aged 10 years, suffered a severe injury when a heavy wine cask fell on her chest. Twenty-one years later, at autopsy, a complete rupture of the right main bronchus 3 cm. below the bifurcation was found. The right lung was completely atelectatic, and, while the left showed marked tuberculosis, the right was entirely free from involvement.

B. R. LOVETT.

**THE FUNCTION OF LYMPHOCYTES.** S. BERGEL, *Virchows Arch. f. path. Anat.* **266:820**, 1928.

The author states that lymphocytes have a lipolytic function, whereas leukocytes do not. Lipoid substances are seen to be taken up and digested by lymphocytes, which therefore are of greatest importance in tuberculous and syphilitic infections. There is no parallelism, however, between the number of lymphocytes and the lipase content of the blood. The lipase is specific for the antigen which calls it forth.

B. R. LOVETT.

**CERTAIN FEATURES OF THE MORPHOLOGIC PATHOLOGY OF ENDEMIC GOITER.** D. MARINE, *Transactions of the International Conference on Goiter*, Bern, Switzerland, Aug. 24-27, 1927. Edited by Hans Huber, Bern, 1928.

The cycle of morphologic changes in the thyroid is essentially the same in all animals and consists of hypertrophy and hyperplasia followed either by exhaustion atrophy (cretinism and myxedema) or by involution to the colloid or resting stage (recovery). Exhaustion atrophy occurs only in the severest grades of uncompensatory hyperplasia, while involution to colloid goiter is the usual termination of active hyperplasia.

Of the numerous secondary changes that occur in goiter, the development of adenomatous nodules is most prominent in goiter in man. Struma nodosa is rarely seen in the lower animals. The belief is expressed that these nodules arise from differentiated thyroid tissue during the late stages of compensatory hypertrophy because of different rates of growth. These nodules tend to repeat the same morphologic cycle as nonadenomatous tissue although somewhat modified. There is abundant evidence that these adenomatous growths can produce thyroxine. There is no evidence that true tumors can produce this substance.

Thyroid hyperplasia (goiter) is a compensatory process dependent on a relative or absolute deficiency of iodine.

AUTHOR'S SUMMARY (A. HELLWIG).

**PATHOLOGIC ANATOMY OF THE MALIGNANT GOITER AND, OF THE THYROID GLAND OF CRETINS.** C. WEGELIN, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-27, 1927. Edited by Hans Huber, Bern, 1928.

The malignant tumors of the thyroid gland are far more frequent in countries in which the goiter is endemic than in goiter-free regions.

The epithelial forms of the malignant goiter may be designated as carcinoma from a biologic point of view. Their malignancy is chiefly evident by the formation of metastasis. Histologically these neoplasms are often not ordinary cancers, but more differentiated and typically formed tumors which also always appear in the form of nodules. The highest degree of differentiation is reached by the metastasizing adenoma, a lesser one by the Langhans' proliferating adenoma and the least degree by the simple carcinoma. There are transitions which unite all these forms. They metastasize only after invasion of the blood vessels especially of the capsular veins. The age of the patient must be considered as another important factor.

The malignant epithelial neoplasm, as well as the sarcoma and hemangio-endothelioma, often originate in the nodules of old adenomas.

The study of histogenesis thus shows a connection of the malignant tumors with the common endemic nodular goiter. Efficacious prophylaxis of the goiter will therefore be able to diminish the incidence of malignant goiter.

Endemic cretinism is to be found only in districts in which goiter is endemic and in which the endemic has reached a high degree.

The thyroid of the cretin contains, as a rule, adenomatous nodules which, however, vary greatly in size. Almost without exception, they are parenchymatous and contain little or no colloid.

The structure of the thyroid tissue proper between the nodules shows characteristic changes, the epithelial cells undergoing a more or less severe degeneration. The colloid of the acini is scanty, chiefly basophil and the connective tissue is increased, forming a marked sclerosis. These changes are found in the highest degree in the atrophic thyroid glands of dwarf cretins.

The degeneration of the epithelial tissue of the gland begins early in the cretin. His thyroid gland functions in an inferior way, although part of its functions may be taken over by the adenomas.

The whole organism of the cretins is influenced by a hypothyroidism of different degree. The changes in the other organs show considerable resemblance or conformity with the changes seen in congenital or acquired athyreosis.

Regarding the etiology of endemic cretinism, external injuries of the thyroid gland, as well as hereditary factors, must be taken into account. The nature of the external factors is not yet known. The assumption that cretinism is a recurrence to the type of the primitive human races is not proved.

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In order to understand the morphologic and etiologic genesis of goiter it is necessary to grasp the fact that the biologic curve of the goitrous thyroid is parallel to that of the nongoitrous thyroid gland. The curve of the goitrous thyroid is, however, more elevated than the other. From the morphologic point of view, goiter is a real hyperplasia of the thyroid.

In the curves of age incidence, there are several corresponding sharp rises to be noted, viz., the swelling or goiter of infancy, puberty and advanced age. In point of origin, they are to be distinguished as follows: (a) in the goiter of infancy, there is in addition to increased new formation a simultaneously increased moisture of the whole parenchyma. (b) The swelling or goiter of puberty is of chief importance, since on its degree essentially depends the intensity of the later

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developed adenoma. (c) In advanced age, a retrogression of the proliferating goiter of goiter may come to pass.

The biologic curve of the thyroid, goitrous or otherwise, is deformed by the development of the so-called adenomas. The germ of them occurs in all thyroids. In districts in which goiter seldom occurs they develop slowly and only to a certain size, in goitrous countries much faster and on occasion up to the size of a child's head or even larger. This intensified development of the tumors, the so-called struma nodosa, depends especially on the enhanced metabolism of the goitrous thyroids.

In point of histologic origin, the adenomas present either an unphysiologic growth with immature (parenchymatous goiter) or riper stages (colloid goiter). According to the type of involution to which these tumors generally tend, the names of fibrous, calcified, hemorrhagic, cystic goiter are given. The nodular goiter originates commonly at or after puberty.

The question of etiology must be considered with that of the source of the general increase in weight of the thyroid in goitrous regions. Comparative histology supports the view that here an exogenous factor encountered in the surroundings is at fault, which leads to enhanced physiologic growth. According to chemical analysis of goitrous and nongoitrous thyroids, it must be assumed that the thyroid as a whole is continually striving for certain iodine content. When the supply is deficient, the absorbent surface of the thyroid increases through further growth of the parenchyma. Conformably thereto the percentage of iodine content is similar in the goitrous thyroid. Experiment indicates that it is not simply iodine deficiency which comes into play, but disturbed equilibrium between iodine and other substances.

The question of the periodic swelling or increase in size of the thyroid (that of pregnancy, infancy, puberty, advanced age and their respective forms of goiter) is independent from that of the goitrous swelling. Here factors at once endogenous and physiologic—among them perhaps an insufficiency of iodine metabolism or disturbances of iodine equilibrium connected with growth—have to be reckoned with.

A sharp distinction must be drawn between endemic goiter and the thyroid of exophthalmic goiter. In this case the causative factor is endogenous and, in contrast to the swelling mentioned, pathologic. Simultaneous diseases of the thymus, suprarenal glands and lymphatic system warrant the conclusion that this cause attacks the nervous system and not the thyroid. The thyroid in cases of exophthalmic goiter is characterized by a special hyperplasia in the interior of the individual follicles. Intermediate stages occur between the hyperplasia in exophthalmic goiter and the parenchymatous goiter.

In contrast to the thyroid of exophthalmic goiter which shows marked symptoms of hyperthyroidism, in the goitrous thyroid it shows rather the picture of hypothyroidism in all stages down to complete cretinism. Only in a few cases does goiter exhibit hyperthyroidism; such are usually late forms of the goiter of puberty or so-called toxic adenoma.

Provided no signs of cretinism occur, endemic goiter displays no secondary influence on other systems. Goitrous heart, implying that the heart muscle is damaged by thyroidal toxins or bacterial toxins, is, according to morphologic evidence, nonexistent.

AUTHOR'S SUMMARY (A. HELLWIG).

### Pathologic Chemistry and Physics

LIPID STUDIES IN XANTHOMA. U. J. WILE, H. C. ECKSTEIN and A. C. CURTIS, *Arch. Dermat. & Syph.* 19:35, 1929.

There is an excess of fatty substances other than cholesterol in the lesions of xanthoma. The cholesterol amounts to only 16 per cent of the entire content of lipids and only 2 per cent of the content of solids. Xanthoma frequently occurs

without cholesteremia. Xanthoma is not due primarily to cholesterol, for this substance occurs in the lesions in a normal value, whereas the other lipids are in increased amounts. The high cholesterol content of the blood in the lipemia of diabetes is an associated factor in the disordered fat metabolism and not the primary cause of xanthoma. In the absence of diabetes, marked increases in the alimentary fat do not appear to influence the formation or growth of xanthoma lesions. Apparently, the best treatment for xanthoma, with or without glycosuria, is a restricted diet as with obesity.

AUTHORS' SUMMARY.

THE REACTION OF THE BLOOD IN CANCER. H. MILLET, *J. Biol. Chem.* **82**:263, 1929.

The hydrogen ion concentration of the blood in persons with cancer appears to be within the normal range.

ARTHUR LOCKE.

EFFECT OF DISEASE ON THE LIPID DISTRIBUTION IN HUMAN LIVER TISSUE. E. R. THEIS, *J. Biol. Chem.* **82**:327, 1929.

Normal liver tissue in man has a phospholipid neutral-fat ratio of approximately 3/2. This ratio becomes progressively decreased during the advance of pneumonia, tuberculosis and fatty degeneration.

ARTHUR LOCKE.

RELATION OF CHROMATIN TO HEMOGLOBIN AND BILIRUBIN. HERMAN H. RIECKER, *J. Exper. Med.* **49**:937, 1929.

Attention is directed to the diversity of opinion among investigators regarding the site and the manner of the formation of hemoglobin in the body, and its relation to bile pigment metabolism. It is probable that, in forming new hypotheses on this subject, the earlier work of A. B. Macallum on the relation of chromatin to the formation of hemoglobin has not received sufficient consideration. It has been shown by means of microchemical stains of the bone-marrow cells for iron, that the iron content of the hematoblast is increased during the rapid production of hemoglobin in simple anemia. This fact is compatible with the work of Macallum, who believed that hemoglobin is derived from the chromatin of the hemoblast. It does not support a theory that hemoglobin is formed as a part of a circulating pigment. It is suggested that bilirubin is derived from the chromatin of body cells through the intermediary stages of the respiratory pigments, hemoglobin and cytochrome, from erythrocytes and other cells, respectively.

AUTHOR'S SUMMARY.

PHYSIOLOGIC CHEMISTRY OF SENESCENCE OF TISSUES (CORNEA). M. BÜRGER and G. SCHLOMKA, *Ztschr. f. d. ges. exper. Med.* **61**:465, 1928.

Previous contributions dealt with chemical changes in cartilage and lens during senescence. The main changes found were diminution of water content and deposition of cholesterol, calcium and other substances. Similar results were obtained in examination of the cornea in cattle. There was demonstrated a progressive diminution of the water content and a corresponding increase of dry substance. The nitrogen content of the dry substance was decreased, the cholesterol content increased. The authors believe that the formation of arcus senilis is determined primarily by condensation of the tissue (diminution of water content) and secondarily by deposition of cholesterol and lipoids. This view is opposed to that of Versé and his collaborators, who regard the formation of arcus senilis primarily as an expression of disturbed cholesterol metabolism.

BALDUIN LUCKE.

THE POTASSIUM, CALCIUM AND MAGNESIUM CONTENTS OF CEREBROSPINAL FLUID. BELA EISLER, *Ztschr. f. d. ges. exper. Med.* **61**:549, 1928.

The potassium, calcium and magnesium contents in the cerebrospinal fluid and their relative ratios were determined for 154 patients. In the acute, purulent forms

of meningitis (twenty-nine cases), little change was found in the amounts of potassium and calcium, but the amount of magnesium was increased several fold. In tuberculous meningitis (fifteen cases) there was an increase of potassium to from 15 to 20 per cent above the normal, and a diminution of calcium. No changes were found in twenty-eight cases of serous meningitis. There were no constant changes in thirty-eight cases of cerebrospinal syphilis. In two cases of paresis there occurred an increase of potassium and magnesium, and a decrease of calcium after treatment with malarial parasites. In patients with tetany and spasmodophilia, the calcium was particularly low.

BALDUIN LUCKE.

#### RELATIONS OF BLOOD PRESSURE, BLOOD VOLUME AND SIZE OF HEART.

ALFRED BEHRENS and WALTER LAMPE, *Ztschr. f. d. ges. exper. Med.* **61**:651, 1928.

From clinical and roentgenologic observations, it is apparent that the size of the heart depends to a certain degree on the blood volume. Thus, in nearly exsanguinated patients (hemorrhage from gastric ulcer), the cardiac shadow increased in size as the general condition improved; this change in cardiac size cannot be explained as hypertrophy. The interrelation of blood pressure, blood volume and size of heart was investigated experimentally in dogs and rabbits. In these animals, a diminution of the blood volume (through venesection) led to a reduction in the size of the cardiac shadow and to a lowering of the blood pressure. A return to the normal could immediately be brought about by an intravenous injection of colloidal solutions, such as acacia. A sudden increase of blood volume was obtained by the rapid intravenous injection of 20 per cent acacia and similar solutions; this led to an increase of cardiac size and a rise in blood pressure.

Gradual injection of fluid did not alter blood pressure or cardiac size.

BALDUIN LUCKE.

#### POSTMORTEM ACIDITY OF THE BLOOD. OTTO GSELL, *Ztschr. f. d. ges. exper. Med.* **63**:18, 1928.

Electrometric determinations of  $p_H$  were made on the blood obtained post mortem from a series of patients and laboratory animals. It was found that a definite decrease of  $p_H$  occurs after death. The greatest increase in acidity takes place in the first hour after death; after from three to four hours, a maximum is generally reached at which the  $p_H$  is approximately 1 less than it was immediately before death. Corresponding changes in the hydrogen ion concentration are to be found in the various organs. The changes in the blood are due to diffusion of acid from the various organs. The  $p_H$  decrease in the first hour after death is to be attributed to the anoxybiotic phase of carbohydrate metabolism, which continues for a short while after death, and hence represents the final expression of vital processes. Rigor mortis, postmortem clotting of blood and possibly the clouding of the parenchymatous tissues are the sequels of postmortem acidity. From about the fourth to the sixth hour after death, the hydrogen ion concentration of the blood undergoes no constant change; there is sometimes a shift toward the alkaline, at other times a shift toward the acid region. These fluctuations are determined by autolytic processes. It follows that  $p_H$  determinations made three or four hours after death will not give constant results.

BALDUIN LUCKE.

#### PATHOLOGY OF BLOOD PROTEINS. G. VON FARKAS, *Ztschr. f. d. ges. exper. Med.* **63**:64, 1928.

Total plasma protein was determined by Kjeldahl's method; the relative proportions of the fractions (albumin, globulin, fibrinogen) were estimated by nephelometric methods. The author emphasizes that marked fluctuations may occur even during health. He gives a table to show the variations observed in healthy adults (number of persons examined is not stated): total protein, from 6.1 to 8.7 Gm.

per cent; albumin, from 3.6 to 5.5 Gm.; globulin, from 1.4 to 3.9 Gm.; fibrinogen, from 0.2 to 0.3 Gm. Two examples of diurnal variation are given, showing slight fluctuations of the various values. In patients with compensated cardiac disease, normal levels were found. In those with decompensated cardiac disease with edema there was reduction in the total amount of protein (total protein, 5.87 Gm.; albumin, 3.4 Gm.; globulin, 2.22 Gm.; fibrinogen, 0.53 Gm.). In cases of nephrosis there was the usual reduction of total protein with an absolute reduction in albumin, and an increase in globulin and fibrinogen. In some cases of cachexia (a case of severe tuberculosis is given as an example), the total protein may be increased to over 10 Gm. per cent.

In cases of hypertension of nephrogenic origin (nephrosclerosis) there was an increase in total protein due to increase in the albumin fraction.

After injection of antigens there occurred an increase in total protein, due, mainly, to an increase in the globulin and fibrinogen fractions. Similar results were obtained after intramuscular injections of sulphur.

BALDUIN LUCKE.

PHYSIOLOGIC CHEMISTRY OF SENESCENCE OF TISSUES (SKIN). M. BÜRGER and G. SCHLOMKA, *Ztschr. f. d. ges. exper. Med.* **63**:105, 1928.

Previous studies dealt with "bradytrophic" tissues, i.e., tissues (cartilage, lens, cornea) not possessing an independent blood supply and nourished by diffusion of fluids from adjacent tissues. The changes developing with age in such tissues were, primarily, a condensation, as evidenced by decrease of water content, and, secondarily, depositions of cholesterol, calcium, etc. The present study was undertaken in order to determine a possible chemical difference in a tissue having a rich blood supply, the skin. The material was removed from the upper thoracic region within twenty-four hours post mortem and the subcutaneous tissue was carefully dissected off. The water, nitrogen and cholesterol contents were determined. The water content was found to decrease with age; the nitrogen content showed but slight changes and the cholesterol content a definite and gradual decrease. This diminution of cholesterol is in striking contrast with the results obtained in the examination of cartilage, cornea and lens.

BALDUIN LUCKE.

THE IODINE CONTENT OF HUMAN ORGANS. BRUNO BUCHHOLZ, *Ztschr. f. d. ges. exper. Med.* **63**:188, 1928.

Extensive tables are given showing the results obtained by other investigators, as well as by the author. All tissues in man contain iodine, but there is no constant level of the iodine in the different organs, except possibly in the thyroid gland. The iodine of the thyroid gland constitutes from about  $\frac{1}{6}$  to  $\frac{1}{4}$  of the total iodine of the body. All glands of internal secretion contain a higher level of iodine than the other organs; this is particularly true of the ovaries and the suprarenal glands. There appears to be a definite relation between the iodine content and the functioning of organs of internal secretion; thus the ovary after the menopause practically loses its iodine content.

BALDUIN LUCKE.

PHYSICOCHEMICAL CHANGES OF THE BLOOD AND HISTOLOGIC CHANGES IN THE KIDNEY IN EXPERIMENTAL NEPHRITIS. N. ISHIYAMA, *Ztschr. f. d. ges. exper. Med.* **63**:699, 1928.

Determinations were made of the total serum protein and the protein fractions of the nonprotein nitrogen, and of the sedimentation rates of erythrocytes in a series of normal rabbits, as well as rabbits fed on a diet high in protein (a mixture of soja beans and a vegetable protein preparation called "legmon"). The daily amount of protein ingested by each animal over a period of from thirty-three to sixty-seven days was from 26.7 to 35.6 Gm. Normal values are given for ten adult male, and an equal number of female, healthy rabbits. (The values stated

include total serum protein, fibrinogen, euglobin, pseudoglobulin, globulin, albumin, nonprotein nitrogen and the sedimentation rates of the erythrocytes.)

No differences were found between the sexes, in contrast with the definite difference that is normally present in man. Histologically, the kidneys of the animals disclosed the following changes: hypertrophy and hyperemia of the glomeruli, atrophy of convoluted tubules and overgrowth of stroma (details are not stated). The urinary changes consisted of a diminution of urinary output, a slight albuminuria and, in some animals, a slight increase of nonprotein nitrogen. There was also an indefinite increase in total serum protein. No important changes were observed in the sedimentation rates of erythrocytes.

BALDUIN LUCKE.

#### EFFECT OF HISTAMINE SHOCK ON BLOOD CALCIUM AND POTASSIUM IN DOGS.

GUSTAV KUSCHINSKY, *Ztschr. f. d. ges. exper. Med.* **64**:563, 1926.

During histamine shock, the potassium was found greatly increased in plasma, or serum; it was less markedly increased in whole blood. The calcium was increased in plasma and serum, but sometimes decreased in whole blood. These results correspond to changes observed in anaphylactic shock.

BALDUIN LUCKE.

#### CATALASE CONTENT OF THE BLOOD FROM DIFFERENT CAPILLARY REGIONS.

F. VON KRÜGER, *Ztschr. f. d. ges. exper. Med.* **64**:680, 1927.

The catalase number of the blood was determined for adults and two boys by the micromethod of Bach and Zubkova (*Biochem. Ztschr.* **125**:283, 1921). Blood from the lobe of the ear and from the tip of the finger had the same catalase content. Normally, the catalase number varied directly with the number of erythrocytes. The catalase index (catalase number divided by numbers of erythrocytes in millions per cent) of normal persons fluctuates within narrow limits (2.8 to 3.8); the mean value at 20 C. is 3.2. For a given person, the catalase index, under physiologic conditions, represents a constant. The results obtained are contrary to those of Bischoff (*Arch. f. Kinderh.* **82**:189, 1927), who reported considerable variations of the catalase content of the blood from different capillary regions. The present author attributes these variations to errors of method.

BALDUIN LUCKE.

#### THE REACTION OF CELLS AND TISSUES. HELMUT PETOW and ERICH WITTKOWER, *Ztschr. f. d. ges. exper. Med.* **64**:736, 1929.

Mice and guinea-pigs received repeated subcutaneous or intraperitoneal injections of various indicators (neutral red, phenol red, brom-thymol blue, brom-cresol purple, methyl red, alizarin, brom-phenol blue). The animals were killed thirty minutes after the final injection and the various organs were examined grossly, as well as microscopically, in free-hand or frozen sections and teased preparations. The cells exhibited changes in color within a few minutes after the preparations were made in the sense that the colors appeared turbid so that shades and tints could not be correctly estimated. Certain dyes, especially alizarin, remained unchanged after treatment of the tissue with formaldehyde, thus permitting the fixation of tissues prior to examination. This article is not suitable for abstracting because of the extensive details on the staining reactions obtained by different indicators and in different cells. However, it contains a wealth of information for those working with vital dyes. In agreement with the results obtained by Miss Schmidtman (previously abstracted in the ARCHIVES), the  $p_H$  of most cells was found to lie between 6.5 and 7. In the kidney, the  $p_H$  of the cortical cells was fairly constant at about 6.7, while the reaction of the medullary cells varied greatly. An excellent bibliography is appended to this paper.

BALDUIN LUCKE.

## Microbiology and Parasitology

TYPHOID INFECTION BY RECTUM. C. R. HENEY, *Am. J. Pub. Health* **19**:166, 1929.

Thirteen cases of typhoid fever are reported as resulting from the use of a rectal drip apparatus without proper sterilization. The original source was a patient who developed typhoid fever on the fourteenth day after admission.

PNEUMOCOCCI HITHERTO CALLED GROUP IV. GEORGIA COOPER, MARGUERITE EDWARDS and CAROLYN ROSENSTEIN, *J. Exper. Med.* **49**:461, 1929.

The pneumococci hitherto known as group IV have been separated into ten types which have been designated by Roman numerals from IV to XIII. These have been correlated as far as possible with the types described by others. The prevalence and mortality of cases due to each type have been estimated in the limited number of cases studied. Laboratory tests indicated that therapeutic anti-serums for types I, II and III have little protective power against the recently separated types. Monovalent antisera of high agglutinative and protective power were prepared in rabbits for each type. Several monovalent antisera, each specific for a type, which are suitable for agglutination and experimental therapeutic use, have been obtained by immunizing horses. An antiserum prepared for one type had little crossprotective power against other types. A study of the possibility of preparing a suitable refined and concentrated polyvalent antiserum has been begun.

AUTHORS' SUMMARY.

LACTASE AND LIPASE OF THE COLON BACILLUS. LOUIS LOWENSTEIN, WILLIAM L. FLEMING and JAMES M. NEILL, *J. Exper. Med.* **49**:475, 1929.

Colon bacilli possess endocellular heat-labile lactase and lipase enzymes which remain operative in sterile filtered solutions of the intracellular substances obtained through physical disintegration of the bacillary bodies. The demonstration of the lactase and detection of the hexose products of its action constitute experimental evidence that hydrolysis of the disaccharide is the first step in the fermentation of lactose by colon bacilli.

AUTHORS' SUMMARY.

OBSERVATIONS ON THE OXIDATION-REDUCTION PROPERTIES OF STERILE BACTERIOLOGICAL MEDIA. RENÉ DUBOS, *J. Exper. Med.* **49**:507, 1929.

Sterile plain broth contains an active oxidation-reduction system, the characteristics of which have been analyzed. Intensity factor: Under petrolatum seal, the lot of broth used in these experiments reaches a reduction potential corresponding to reduced indigo disulphonate ( $rH = 10$ ). All the indicators with a more positive  $E'$  are reduced, the others are not affected. It seems probably that fresh broth, which has not undergone oxidation by molecular oxygen, would give a higher reduction potential. Capacity factor: The maximum amounts of different indicators that can be reduced correspond to equimolecular concentrations. This seems to indicate either (a) that the broth does not contain several "independent" reducing systems (at least in appreciable amounts), or (b) that these hypothetical "independent" systems all have about the same reduction potential. Time factor: The different indicators of oxidation-reduction potentials are reduced in the order of the electromotive series. Nature of the system: The system seems to be reversible (this not excluding the possibility of irreversible autooxidations) and does not appear to be of the nature of a sugar. The relation of these phenomena to the cultivation of different species of bacteria will be reported later.

AUTHOR'S SUMMARY.

NON-HEMOLYTIC STREPTOCOCCI AND ACUTE RHEUMATIC FEVER. ROBERT N. NYE and DAVID SEEGAL, J. Exper. Med. **49**:539, 1929.

Blood cultures from twenty-five cases of acute rheumatic fever were negative for nonhemolytic streptococci of both the alpha and gamma types. Nonhemolytic (gamma type) streptococci were frequently recovered from the throats of patients with this disease. Similar organisms were recovered just as frequently from the throats of normal persons. Although these nonhemolytic streptococci were morphologically and culturally identical, not only among themselves, but also when compared with stock Small and Birkhaug strains, all, including the latter, have failed to show any noteworthy degree of homogeneity. Representative strains of these streptococci have proved to be relatively nonpathogenic for rabbits following intravenous injection. These organisms, with a few exceptions, have failed to produce soluble skin-reacting toxins comparable to Birkhaug's standard test toxin. The foregoing facts seem to invalidate the assumption that any of these non-hemolytic streptococci play a specific rôle in the etiology of acute rheumatic fever.

AUTHORS' SUMMARY.

THE INITIATION OF GROWTH OF CERTAIN FACULTATIVE ANAEROBES AS RELATED TO OXIDATION-REDUCTION PROCESSES IN THE MEDIUM. RENÉ DUBOS, J. Exper. Med. **49**:559, 1929.

The growth of many pathogenic organisms in plain meat infusion broth is possible only when a large inoculum is used. This requirement is much less strict when the broth cultures are incubated under anaerobic conditions, in fresh mediums recently boiled or autoclaved, in fresh mediums reduced by means of hydrogen, or to which small amounts of cysteine or of blood have been added. It is suggested that this can be accounted for by assuming that the bacterial species under consideration can multiply only in mediums the oxidation potential of which is below a critical value. The favorable growth conditions obtained by the procedures already enumerated may be attributed to the establishment of a proper reduction potential in the medium; the same result is obtained by using a large inoculum, owing to the reducing properties of bacterial cells.

AUTHOR'S SUMMARY.

THE RELATION OF THE BACTERIOSTATIC ACTION OF CERTAIN DYES TO OXIDATION-REDUCTION PROCESSES. RENÉ DUBOS, J. Exper. Med. **49**:575, 1929.

Oxidized indophenols and methylene blue (methylthionine chloride, U. S. P.) are bacteriostatic for pneumococcus and hemolytic streptococci of human and bovine origin, while the indigoes, malachite green and litmus are not toxic. 2-chloroindophenol, the most positive of the indicators of oxidation-reduction potentials used, is also the only one to have a bacteriostatic action on cheese strains of *Streptococcus hemolyticus*. Methylene blue and the indophenols are no longer bacteriostatic when present in a reduced form in a medium capable of maintaining them in such a condition. A comparison of these results with the growth in plain broth of the organisms studied suggests that the "inhibiting" dyes "poise" the medium at an oxidation potential outside the range in which the inhibited organisms can grow. The validity of this hypothesis is discussed. The significance of these observations for the use of dyes in therapeutics is considered.

AUTHOR'S SUMMARY.

TOXIC SUBSTANCES OF BACILLUS TYPHOSUS. GREGORY SHWARTZMAN, J. Exper. Med. **49**:593, 1929.

It is shown in this paper that homologous immune serums are able to neutralize the *B. typhosus* skin-preparatory factors. The neutralization experiments were performed on a large number of rabbits, at least ten rabbits which showed positive control reactions being used for the titration of each serum. The rabbits into

which the mixtures of *B. typhosus* culture filtrates with immune serums were injected can be divided into the following categories; those showing complete neutralization in highest dilutions (HN), those showing complete neutralization only in lower dilutions (LN) and those showing no neutralization (NN). The results indicate that the potency of a given serum as measured by the method already outlined has a direct relation to the reactions obtained in these groups of rabbits. For practical purposes, the highest dilution of the serum which gives complete neutralization of the *B. typhosus* skin-preparatory factors (HN titer) may be taken as the actual titer of the serum as expressed in terms of their neutralization. The occurrence of a phenomenon suggestive of the prozone reaction is demonstrated. It also appears that the filtrates possess an antigenicity equal to that of dead and live bacteria. The studies on normal serums bring out the fact that normal serums fail to neutralize the *B. typhosus* skin-preparatory factors unless agglutinins can be demonstrated for *B. typhosus*. No normal serums have thus far been obtained which neutralized the skin-preparatory factors yet contained no *B. typhosus* agglutinins, but there were serums which contained these agglutinins but failed to neutralize the skin-preparatory factors. Some of the normal animals whose serums failed to neutralize the skin-preparatory factors were subsequently injected with *B. typhosus* culture filtrate and responded with neutralizing serums of high titer. Several heterologous serums were also investigated, namely, scarlet fever, erysipelas, Shiga bacillus, Flexner bacillus, Mount Desert bacillus, *B. coli* and *B. avicida*. These did not neutralize the *B. typhosus* skin-preparatory factors. On the other hand paratyphosus A and B serums produced neutralization in various proportions. And the rabbits into which the serum-filtrate mixtures were injected could also be divided according to the results obtained into the same three groups as those with *B. typhosus* serums. It is not known yet whether this neutralization is a group reaction or whether the skin-preparatory factors are identical with those of *B. typhosus*. It would appear from these studies that a method is available for the quantitative titration of substances in the serum which neutralize the skin-preparatory factors of local skin reactivity to *B. typhosus* culture-filtrates. It should be emphasized that it is possible to control the individual susceptibility of rabbits to this phenomenon. The method should permit of considerable accuracy in the quantitative titration of the neutralizing properties of a serum when a standardized procedure is developed. Experiments are under way to determine whether the method can be applied to the preparation of therapeutic serums. Work is also in progress to determine the effect of specific antisera on *B. typhosus* skin-reacting factors introduced by the intravenous route.

AUTHOR'S SUMMARY.

TRANSMISSION OF FOWL-POX BY MOSQUITOES. I. J. KLIGLER, R. S. MUCKENFUSS and T. M. RIVERS, J. Exper. Med. **49**:649, 1929.

*Culex* and *Aedes* mosquitoes are capable of transmitting fowlpox from diseased to healthy susceptible chickens. The mosquitoes remain infectious for at least fourteen days following a meal on diseased fowls.

AUTHORS' SUMMARY.

HERPES ENCEPHALITIS IN CEBUS MONKEYS. HANS ZINSSER, J. Exper. Med. **49**:661, 1929.

Herpes virus, which ordinarily produces in *Cebus olivaceus* monkeys an acutely fatal encephalitis closely resembling in time, symptoms and pathology the acute, herpetic disease of rabbits, may—in more resistant individual monkeys—lead to a more prolonged malady which, while unquestionably produced with herpes virus, simulates with considerable accuracy the human disease of acute encephalitis, in symptoms, in course and in pathologic changes.

AUTHOR'S SUMMARY.



A STRAIN OF *BACILLUS ABORTUS* FROM SWINE. THEOBALD SMITH, J. Exper. Med. **49**:671, 1929.

The outbreak of infectious abortion in swine, probably the first reported from the eastern United States, was associated with a strain of *Bacillus abortus* growing rapidly on ordinary nutrient agar slopes without seal and presenting certain slight pathologic deviations from the bovine form of disease in guinea-pigs such as the occurrence of necrotic, suppurating foci in spleen and lymph nodes. Agglutination tests, comprising both cross-agglutination and absorption procedures, failed to distinguish the strain from the bovine type. The gross appearance of the fetuses from this outbreak was normal. The shreds of placentas obtainable indicated slight erosion of the chorionic epithelium and some exudation. The specific bacilli were widely disseminated in the tissues of the fetuses. The pathogenic action of this swine strain on guinea-pigs was evidently much feebler than that of most earlier swine strains as reported and it approached more closely that of bovine strains. The culture fed to a pregnant sow failed to produce abortion, possibly because of the advanced stage of pregnancy. The organism was not recovered from the uterus but was found in the sow's milk.

AUTHOR'S SUMMARY.

DIFFERENTIATION BETWEEN SOME TOXIC SUBSTANCES IN ANAEROBICALLY PRODUCED AUTOLYSATES OF PNEUMOCOCCI (TYPES I AND II). JULIA T. PARKER, J. Exper. Med. **49**:695, 1929.

The necrotizing and lung-toxic principles present in certain anaerobically prepared autolysates of pneumococcus types I and II are similar in respect to extreme sensitiveness to heat and to oxidation, and to their ability to be neutralized by the same anti-autolysate serums. These two poisons differ, however, in their ability to be adsorbed or inactivated by red cells; the lung-toxic principle being adsorbed or inactivated by such procedure while the necrotizing principle is not. Since pneumococcus hemotoxin is present in the anaerobic autolysates and is also adsorbed by red cells, it seemed possible that it was this substance in the autolysates which caused the diffuse lesions in the lungs and death of guinea-pigs. However, it was found that the intratracheal injection of pneumococcus hemotoxin prepared by the method of Avery and Neill only occasionally produced the characteristic reaction caused by the intratracheal injection of the anaerobic autolysates. From these experiments, we believe, therefore, that the necrotizing and lung-toxic principles, and probably the pneumococcus hemotoxin also, are all separate entities in the anaerobically produced autolysates described.

AUTHOR'S SUMMARY.

SURVIVAL OF THE VIRUS OF POLIOMYELITIS FOR EIGHT YEARS IN GLYCEROL. C. P. RHOADS, J. Exper. Med. **49**:701, 1929.

An instance of successful inoculation of poliomyelitis virus after preservation for eight years in 50 per cent glycerol is reported. The virulence of the material injected remained essentially unchanged during this period. The fact that poliomyelitis virus will survive in glycerol for so great a period may be taken as further indication of the improbability of streptococci as the inciting organisms. Poliomyelitis virus would seem to vary in its resistance to glycerolation. The remarkable persistence of active virus outside of the body may have a bearing on the epidemiology of poliomyelitis.

AUTHOR'S SUMMARY.

SEPTIC SORE THROAT IN 1928 IN MASSACHUSETTS: EPIDEMIOLOGY. HERBERT L. LOMBARD, J. Prev. Med. **3**:81, 1929.

There were between 925 and 975 cases and 48 known deaths in the epidemic of sore throat in "K," Massachusetts, in July, 1928. The attack rate was 221 cases per thousand inhabitants; the death rate was 9.6 per thousand inhabitants. The epidemic was caused by the transmission, through raw milk, of hemolytic streptococci from the infected udder of a cow. The method by which the cow

was infected is unknown, although some evidence points toward a milk handler who was sick. Among the regular users of the infected milk the attack was greater in females than in males, but it shows no significant differences in the various age groups. The incubation period of the disease averaged two days. Over 90 per cent of the cases occurred within an interval of two weeks. Contact probably was responsible for less than 5 per cent of the total cases, but it is impossible to establish this definitely.

AUTHOR'S SUMMARY.

THE INCUBATION PERIOD OF POLIOMYELITIS. W. LLOYD AYCOCK and ELIOT H. LUTHER, J. Prev. Med. 3:103, 1929.

Data bearing on the incubation period of poliomyelitis have been collected from the following sources: milk-borne outbreaks; cases following tonsillectomy; isolated groups of cases in the same locality where contact could not be traced; cases in which a single known contact occurred; certain instances of multiple cases in families in which the individuals had separated before the onset of the disease; and an analysis of all cases observed in 1928 in Massachusetts, with known contact, in which an interval of separation had occurred prior to onset. In all cases in which the time of exposure can be set within narrow limits the apparent incubation falls within a period of from six to twenty days. In all cases in which the last exposure occurred less than six days preceding onset of the secondary case, the duration of exposure is such that the incubation period could likewise have fallen within these limits. In none of the observations reported in this paper was the incubation period necessarily shorter than six days. In some of these observations there is evidence that the infectious period of the disease may extend from the fourteenth day preceding the onset of symptoms to at least the fifth day of the disease. The incubation period observed in the experimental disease in monkeys following inoculation of fully active virus was most often six or seven days, but varied from four to fifteen days. Longer incubation periods were observed following inoculation of modified virus.

AUTHORS' SUMMARY.

THE TRANSFER OF TUBERCULOSIS BY DUST AND OTHER AGENTS. A. EVELYN AUGUSTINE, J. Prev. Med. 3:121, 1929.

The evidence that has been collected suggests that the demonstration of virulent tubercle bacilli in dust collected from the rooms or clothing of patients with open tuberculosis may be used as a measure of the danger to which those in contact with the patient are subjected. Dust from the rooms or clothing of patients who keep themselves clean contain tubercle bacilli much less frequently than dust from uncleanly homes and people. Tubercle bacilli are recovered more frequently from the rooms of women than of men with open tuberculosis, and less frequently from the clothing of women than of men. These relations may be explained by the greater personal cleanliness of women and their inability, when ill, to keep their houses clean. Tubercle bacilli are recovered more frequently from the homes and clothing of colored than of white patients. The number of tubercle bacilli in the sputum of the patient is a factor in determining the presence or absence of tubercle bacilli in surrounding dust.

AUTHOR'S SUMMARY.

"FOOD POISONING" PRODUCED IN MONKEYS BY FEEDING LIVING *SALMONELLA* CULTURES. G. M. DACK, E. O. JORDAN and W. L. WOOD, J. Prev. Med. 3:153, 1929.

*Rhesus* monkeys fed with living cells of two strains of the *Salmonella* group manifested definite and characteristic signs of "food poisoning": watery diarrhea and general malaise with, in some cases, loss of appetite. Recovery was prompt and apparently complete; the specific bacilli were not found in the blood stream. A second attack could be produced in the same animal after a short interval. Monkeys fed with equivalent heat-killed portions of the same suspension showed no symptoms. Likewise, feeding with living cells of *Proteus* and *B. coli* failed to produce any noticeable effect.

AUTHORS' SUMMARY.

THE PATHOGENICITY OF MORGAN'S BACILLUS. LEON C. HAVENS and CATHERINE RIDGWAY, *J. Prev. Med.* **3**:159, 1929.

A group of thirteen cases, presenting clinical symptoms in common, has been described. Evidence is presented pointing to Morgan's bacillus as the etiologic agent.

AUTHORS' SUMMARY.

THERMO-LABILE STREPTOCOCCAL TOXIN WITH CYTOLYTIC EFFECT ON LEUCOCYTES. HILDA A. CHANNON and J. W. MCLEOD, *J. Path. & Bact.* **32**:283, 1929.

The older work on streptococcal toxin in which the general toxic effects of actively hemolytic filtrates are described has been repeated and confirmed. A thermolabile toxin which has a marked lytic action on leukocytes is present in such filtrates when 8 to 10 hour serum broth cultures of actively hemolytic streptococci are used. It is this toxin rather than the thermostable skin toxin which is in all probability responsible for the marked invasive activities of the streptococcus in the animal body. No evidence has been obtained in these investigations to show that the cytolytic effects on red cells and leukocytes are due to distinct toxins. It is quite possible that the action on the leukocytes is evident only when the hemolysin acts in high concentrations.

AUTHORS' SUMMARY.

THE EFFECT OF GOLD PREPARATIONS ON RELAPSING FEVER. G. STEINER and V. FISCHL, *Klin. Wchnschr.* **8**:582, 1929.

The chemotherapeutic index of the disodium salt of 4-sulphonethylamino-2-goldmercaptobenzosulphonic acid and A69 in experimental infections of rats with African relapsing fever is considerably higher than that of neoarsphenamine. With prophylactic doses, the former preparation causes, in contrast with the hitherto known prophylactic ineffective gold preparations, a temporary suppression or attenuation of the infection. During the immune period it is possible with this preparation and A69, to destroy the spirochetes persistent in the central nervous system, while arsphenamine and its derivatives have no effect.

AUTHORS' SUMMARY.

THE ACTION OF BACTERIOPHAGES ON TYPHOID BACILLI. CURT SONNENSCHN, München. med. Wchnschr. **76**:355, 1929.

Specific bacteriophage conferred hemolysin (5 per cent goat's blood agar) properties to fifty-five old and twenty-five new strains of typhoid bacilli grown at 37 C., and none at 22 C. Typhoid bacilli considered nonhemolytic in cultures, like the other gram-negative organisms of the typhoid paratyphoid enteritides group, have a latent property for hemolyzing goat blood agar. The hemolysis occurred not only with the specific typhoid bacillus phage, but also with four polyvalent phages. No hemolysis was observed with paratyphoid B, Breslau, Gartner, and Dysentery (Flexner, Shiga) bacilli and polyvalent phages, although these acting on typhoid bacilli stimulated them to hemolysis. The hemolysis by typhoid bacilli probably is no function of the bacteriophage, but rather a property of the treated typhoid bacilli. The hemolysin effect on goat's blood agar, in addition to the simple phage reaction with specific diagnostic phages, can be applied in identifying typhoid bacilli. For human blood agar the bacteriophage conferred no hemolysin properties to fifteen strains of typhoid bacilli. The hemolysin effect can be used therefore in identifying the kind of blood. Among fifty-six stock strains of *B. typhosus* inoculated directly on goat blood agar there were two hemolyzing strains. Both of these contained, by subsequent tests, active typhoid bacillus phages. A larger material is necessary to determine if all typhoid strains associated with typhoid bacteriophage can be separated from those without, by their

hemolyzing growth on goat blood agar. Among twenty strains of *B. typhosus* recently isolated from the blood and feces, one hemolyzed blood, and it also contained bacteriophage.

AUTHOR'S SUMMARY (IN PART).

THE RESISTANCE OF THE SKIN AGAINST TUBERCLE BACILLI. O. N. PODWYSOTZKAJA and M. A. LANNIKOWA, Ztschr. f. Tuberk. **52**:474, 1929.

Tubercle bacilli were rubbed into the depilated and slightly traumatized skin of guinea-pigs. It was found that when small amounts of bacilli were used, the skin did not show any alterations. Larger amounts caused the development of small nodular lesions and swellings of the regional lymph glands. In massive infections, ulcerations and massive swelling of lymph glands with generalized tuberculosis developed.

MAX PINNER.

EFFECT OF FAT-SPLITTING ENZYME OF GUINEA-PIG LUNG ON TUBERCLE BACILLI. D. KANÓCZ, Ztschr. f. Tuberk. **53**:124, 1929.

The author had previously shown that the pulmonary vein blood contains 30 mg. per cent less fat than the blood of the pulmonary artery. The difference was ascribed to the action of a lipolytic enzyme normally present in the lung. To test the hypothesis that such an enzyme might be a factor in the protective mechanism of the lung against tuberculosis, glycerin extracts of perfused normal guinea-pig lung were made. Such extracts had the property of reducing the fat content of normal guinea-pig blood serum and of removing the lipid envelope of the tubercle bacillus. Bacilli thus treated are claimed to protect the animal against infection when used as a vaccine and to influence favorably the course of an already established experimental infection.

O. T. SCHULTZ.

### Immunology

BLOOD VOLUME IN THE GUINEA-PIG DURING ANAPHYLACTIC SHOCK. C. K. DRINKER and S. WENT, Am. J. Physiol. **88**:479, 1929.

Using the writers' micromethod of blood volume determination in guinea-pigs sensitized to sheep serum, no changes in blood volume could be found accompanying the anaphylactic reaction, if complications due to asphyxia were prevented by careful adjustment of artificial respiration.

H. E. EGGERS.

PROTECTION TESTS WITH SERUM OF PERSONS RECOVERED FROM YELLOW FEVER IN THE WESTERN HEMISPHERE AND WEST AFRICA. N. P. HUDSON, J. H. BAUER and C. B. PHILIP, Am. J. Trop. Med. **9**:1, 1929.

It was found that an attack of yellow fever in man induced an immunity transferable to *M. rhesus*. The serum from seven recovered cases in West Africa and that from four cases of eleven tested in the Western Hemisphere protected *M. rhesus* against lethal doses of a West African strain of yellow fever virus injected subcutaneously. Experimental yellow fever was prevented by the use of serum from persons who had the disease in different epidemics.

H. E. LANDT.

THE COMPLEMENT-FIXATION TEST IN DIFFERENT CLINICAL MANIFESTATIONS OF TUBERCULOSIS. T. THJÖTTA and E. GUNDERSEN, Am. Rev. Tuberc. **19**:212, 1929.

Three hundred and twenty-five serums from patients with different manifestations of tuberculosis were examined for complement-fixing ability and are grouped under three headings, pulmonary, surgical and skin tuberculosis, the positive percentages in the three groups being 94.6, 44 and 12.3, respectively.

Only cases of pulmonary tuberculosis showed a relatively high percentage of positive tests. In the other manifestations the positive tests seemed to depend mostly on the presence or preexistence of tuberculosis of the lungs. The complement-fixation test in tuberculosis cannot be compared with the Wassermann test in syphilis, but rather with the same test in other bacterial infections when the specific microbe is used as an antigen.

H. J. CORPER.

NON-SPECIFIC AGGLUTININS IN TUBERCULOSIS. ROBERT A. KILDUFF AND WILLIAM W. HERSOHN, *Am. Rev. Tuberc.* **19**:223, 1929.

Nonspecific, heterologous agglutinins may be produced in tuberculosis for micro-organisms of the typhoid group, and, infrequently, for *Bacillus proteus* X 19. There was no apparent relation between the presence or amount of agglutinins and the character or clinical course of the tuberculous infection. The occurrence of agglutinins for micro-organisms of the typhoid group is not per se conclusive evidence that they are nonspecific, or heterologous in origin, as, in a definite number of such cases, the patient will be found to have had typhoid fever or to have received antityphoid vaccine. Heterologous agglutinin production in pulmonary tuberculosis is of relatively infrequent occurrence and without apparent relation to the clinical course of the disease.

H. J. CORPER.

A CLINICAL STUDY OF TUBERCULIN FRACTIONS PREPARED FROM NON-PROTEIN CULTURE MEDIA. FREDERICK EBERSON and ERNEST WOLFF, *Am. Rev. Tuberc.* **19**:327, 1929.

In the extension of earlier work in which the inadequacy of old tuberculin was stressed and in which tuberculin fractions were prepared from nonprotein culture mediums, detailed analyses of different tuberculous and nontuberculous groups were made, and the conclusion was drawn that a tuberculin preparation described as T. E. (alcohol and ether insoluble) gives better results than ordinary old tuberculin and is more selective as a clinical test material. The preparation and use of this tuberculin fraction are described and discussed.

H. J. CORPER.

CASES OF ERYTHEMA NODOSUM WITH NEGATIVE TUBERCULIN TESTS. ELSA LAGERGREN, *Am. Rev. Tuberc.* **19**:447, 1929.

The author describes six cases of erythema nodosum and believes, as a result of her studies, that an unknown specific infection was the cause of the erythema nodosum.

H. J. CORPER.

ANTIGENIC PROPERTIES OF EVAPORATED MILK. ORAN I. CUTLER, J. A. M. A. **92**:964, 1929.

Heat applied to cow's milk in the process of preparing evaporated milk does not appear to change the antigenic capacity of the casein as determined by anaphylactic reactions. Evidence has been found that there is an alteration in the antigenic properties of whey protein present in raw milk by the heat applied to it in order to evaporate and sterilize cow's milk by the usual methods employed. This is especially seen in a change of specificity, whereby heated whey proteins are less reactive in animals sensitized with raw or pasteurized milk, or with antibodies against pasteurized milk.

AUTHOR'S SUMMARY.

ANAPHYLACTIC EXPERIMENTS WITH GLOBIN. HENRY FRANCIS HOLDEN, *Australian J. Exper. Biol. & M. Sc.* **5**:285, 1928.

The injection of horse globin does not induce fatal anaphylaxis in guinea-pigs. Experiments with the isolated uterus suggest that it becomes sensitive to a protein in the globin solution, which is neither stroma nor serum protein. Quantitative considerations render it unlikely that it is globin.

AUTHOR'S SUMMARY.

**HYPERGLYCEMIA IN ANAPHYLACTIC SHOCK IN THE DOG.** ISOLDE T. ZECKWER and J. ERNEST NADLER, *J. Exper. Med.* **49**:481, 1929.

Nine unoperated dogs showed a rise of blood sugar during anaphylactic shock. In six of these dogs the rise was 60 mg. or over. Six dogs in which one adrenal had long previously been extirpated and the opposite splanchnic nerve cut, showed a low preliminary level of blood sugar, and a relative rise of blood sugar during anaphylaxis, but of less degree than in the unoperated animals. In no case was it greater than 52 mg. Anocemia did not appear to be a complicating factor, as evidenced by determination of the oxygen content of the arterial blood before and during shock. The rise in blood sugar, which occurs in spite of the loss of adrenal activity, is probably due to the venous stasis of the liver seen in anaphylaxis in the dog, because this rise in blood sugar can be simulated in a normal non-sensitized dog by mechanically constricting the hepatic veins for a brief interval. There are, therefore, probably two factors responsible for the hyperglycemia associated with anaphylaxis in the dog, sympathetic stimulation by way of the splanchnic nerves involving the activity of the adrenals, and glycogenolysis resulting directly from venous stasis of the liver.

AUTHORS' SUMMARY.

**THE TOXICITY OF HUMAN SERUM FOR THE GUINEA-PIG.** SUSAN GRIFFITH RAMSDELL and I. DAVIDSOHN, *J. Exper. Med.* **49**:497, 1929.

There are indications of toxicity in all fresh human serum for the guinea-pig; this toxicity tends to disappear after forty-eight hours after bleeding, and its manifestations are strikingly similar to those of the heterophilic antibody in immune rabbit serum; and of an increased toxicity in the serum of human patients treated with antiserums; this is usually coexistent with the production of other antibodies; it tends likewise to disappear in time after treatment; differential absorption experiments indicate that its character is heterophilic, and its manifestations differ from those of anaphylaxis in that certain circulatory effects—hemorrhage and increased edema in the lungs and distention of the right heart—are added to the usual observations in true anaphylactic deaths.

AUTHORS' SUMMARY.

**REACTIONS OF RABBITS TO NONHEMOLYTIC STREPTOCOCCI.** C. L. DERICK and HOMER F. SWIFT, *J. Exper. Med.* **49**:615, 1929.

Accompanying and following the evolution of a secondary reaction in the skin of rabbits after inoculation with suitable doses of certain nonhemolytic streptococci there quickly develops a general state of hypersensitiveness or allergy toward these streptococci. This state is made evident by ophthalmic reactions following corneal inoculations, by much increased reactivity of the skin following intracutaneous reinoculations, and by lethal reactions, resembling tuberculin shock, following intravenous inoculations. In a given hypersensitive rabbit there is a rough parallelism in the intensities of these different kinds of reactions. This type of hypersensitiveness or bacterial allergy does not follow primary intravenous inoculation of rabbits with comparable doses of the streptococci employed. As the development of this type of hypersensitiveness or bacterial allergy seems to accompany the production of focal lesions of a certain intensity, it is probable that in these foci are produced the substances or conditions which lead to this type of bacterial allergy.

AUTHORS' SUMMARY.

**THE ALLERGIZING CAPACITY OF DIFFERENT STRAINS OF INDIFFERENT STREPTOCOCCI.** C. H. HITCHCOCK and HOMER F. SWIFT, *J. Exper. Med.* **49**:637, 1929.

The indifferent streptococci are remarkably efficient allergizing agents when inoculated intradermally into rabbits. This is revealed by the high percentage of secondary reactions which occur in the lesions resulting from the inoculation of small doses of these organisms, and by the relative frequency with which

positive ophthalmic reactions are obtained following sensitization with relatively small doses. This allergizing capacity is most marked in the organisms of Type I and least marked in the noninulin-fermenting strains of Group X. The different resultants emerging from variations in allergizing capacity of streptococci and reactivity of host are clearly demonstrated in this series of experiments.

AUTHORS' SUMMARY.

THE CHEMICAL NATURE OF THE CONSTITUENT IN FOWL SERUM RESPONSIBLE FOR NON-SPECIFIC PRECIPITATIONS. GEORGE S. SCHILLING, *J. Immunol.* **16**:439, 1929.

Examination of precipitated serums, nonprecipitated clouding serums and normal, nonclouding serums of fowls by means of the ultramicroscope revealed fat globules in all cases. The fat globules are present in greater quantities in precipitated and in nonprecipitated clouding serum than in nonclouding serum. Microchemical tests on the precipitates resulting in the agglutination system from the addition of clouding serums show that those precipitates contain quantities of neutral fats and fatty acids. Spontaneous precipitates in fowl serums which induce nonspecific precipitations of serologic antigens, carry a significantly higher iodized oil content than serums which do not produce the cloudy reaction; significant differences in their protein contents do not appear. The constituents in fowl serums responsible for these nonspecific precipitations are indicated to be lipoproteins and neutral fats.

AUTHOR'S SUMMARY.

THE CHANCES OF ESTABLISHING NON-PATERNITY BY DETERMINATION OF BLOOD GROUPS. SANFORD B. HOOKER and WILLIAM C. BOYD, *J. Immunol.* **16**:451, 1929.

From the frequency distribution of blood groups and the laws governing their inheritance the relative usefulness of blood-grouping tests in bastardy proceedings has been calculated with the following result:

Group of Accused Man	Percentage in United States	Probabilities
O .	45	$\frac{1}{3}$
A	42	$\frac{1}{17}$
B	10	$\frac{1}{7}$
AB	3	$\frac{1}{2}$
Unknown	100	$\frac{1}{4}$

QUALITATIVE DIVERSITY OF AGGLUTININ RESPONSE AMONG DIFFERENT RABBITS TREATED WITH THE SAME COMPLEX ANTIGEN (STREPTOCOCCUS SCARLATINAE). SANFORD B. HOOKER, *J. Immunol.* **16**:463, 1929.

The results suggest that qualitative deficiency of antibody response to scarlatinal streptococci occurs rather infrequently among rabbits. It probably explains some of the discrepant reactions obtained by different investigators who have worked with the same strains. The fact that an immune serum may not faithfully and completely reflect the antigenic features of a complex inoculum receives additional confirmation as does the author's previous conclusion that the injected animal's individuality may constitute an important variable in experiments of this kind.

AUTHOR'S SUMMARY.

SYPHILIS WITHOUT CHANCRE AFTER BLOOD TRANSFUSION. E. CONSTANTINESCON and N. VATAMANU, *Ann. de mal. vén.* **24**:161, 1929.

A generalized papular and erosive syphilitic eruption developed in a woman seventy-five days after she had received a blood transfusion. The donor had a mixed chancre at the time of the transfusion.

ECHINOCOCCUS ANTIGENS. J. H. BOTTERI, *Klin. Wchnschr.* **8**:836, 1929.

Protein-free echinococcus antigens of human and animal origin are able to sensitize and cause cutaneous reactions, but are not able to arouse general anaphylaxis. The early reaction in the form of wheals is a sensitive but less specific allergic reaction, dependent on a functional disposition of the skin. Probably the active agents here are the alcohol-soluble simple protein substances. These seem to be identical with the dialyzable substances which pass through the intact echinococcus membrane and cause the skin allergy. The delayed reactions in the form of characteristic specific edema, and the manifestations of general anaphylaxis are caused by the whole antigens, which in vivo reach the circulation of the host from the hydatid fluids by injury of the echinococcus membrane. In complement-fixation the lipoid fraction of the antigen probably is chiefly concerned, with the skin reaction chiefly the protein fraction.

AUTHOR'S SUMMARY.

ANAPHYLAXIS BY THE FORMATION OF SERUM-ISO-ANTIBODIES AFTER REPEATED TRANSFUSIONS OF PATERNAL BLOOD (IDENTICAL GROUP). P. GYÖRGY and E. WITEBSKY, *Klin. Wchnschr.* **8**:195, 1929.

A child, after several transfusions of blood from the father without symptoms, had a severe anaphylactic reaction when another transfusion was made with the father's blood. The blood of both was in group O. EDWIN F. HIRSCH.

PROTECTIVE SUBSTANCES IN EXPERIMENTAL SYPHILIS. ALFRED COHN, *Klin. Wchnschr.* **8**:886, 1929.

The injection of killed spirochetes into animals or into man stimulates the formation of immune substances against the organisms. Why these cannot be demonstrated under the usual conditions of infection needs further investigation.

AUTHOR'S SUMMARY.

BLOOD CHOLESTEROL AND RESISTANCE IN PULMONARY TUBERCULOSIS. V. HINZE, *Ztschr. f. Tuberk.* **52**:199, 1928.

The amount of blood cholesterol in infraclavicular tuberculosis infections is markedly decreased, to about 53 mg. per hundred cubic centimeters. During the period of the primary complex, the cholesterol is somewhat decreased, but rises in the secondary stage. In cases with good allergic response the cholesterol is above the average. In those with poor response it is below the average. Coincident with high cholesterol level, strong tuberculin skin reactions are found. There is no relation between the extent of the lesion and the amount of blood cholesterol.

MAX PINNER.

VARIATION IN COMPLEMENT IN EXPERIMENTAL TUBERCULOSIS OF GUINEA-PIGS. LILLY SANDSTRÖM, *Acta path. et microbiol. Scandinav.* **6**:97, 1929.

In guinea-pigs inoculated by means of tubercle bacilli, fairly regular variations in the complement content of the blood were observed, the titer falling after the inoculation, rising and then falling again toward the end of the life of the animal. Whether this is a specific effect due to the tubercle bacilli or a general reaction for foreign substances is not determined.

## Tumors

THE RELATION OF CANCER TO OLD AGE. JAMES EWING, *Am. J. M. Sc.* **177**:461, 1929.

There are not sufficient data at present to determine the real influence of old age on cancer. Statistics, however, show that the greatest incidence of cancer occurs shortly after middle life and that the liability to the disease, which has



increased greatly during the last two decades, becomes more marked as age advances. Three conditions in the aged require special consideration in dealing with this problem, namely: (1) atrophy of the parenchyma of organs, (2) replacement fibrosis and (3) arteriosclerosis. No one of these is of constant occurrence and there are many complicating factors. Further study is necessary before any conclusions can be reached.

PEARL ZEEK.

CANCER OF THE LUNGS. FREDERICK L. HOFFMAN, *Am. Rev. Tuberc.* **19**:392, 1929.

Cancer of the lung is unquestionably increasing in modern civilized countries. While no entirely conclusive evidence is yet available, there are reasons for believing that the increased frequency is in some way connected with the modern development of road transportation and road conditions which aid in gross atmospheric pollution. There is no definite evidence that smoking habits are a direct contributory cause toward malignant growths in the lungs. Gas warfare and influenza appeared not to be direct contributory causes. The relatively predominating number of men affected is highly significant. There is apparently no relation established between the occurrence of tumors of the lungs and pulmonary tuberculosis.

H. J. CORPER.

THE TETRAPLOID NUMBER OF CHROMOSOMES IN THE MALIGNANT CELL OF THE WALKER RAT SARCOMA NO. 1. MARGARET REED LEWIS and JANE LOCKWOOD, *Bull. Johns Hopkins Hosp.* **44**:187, 1929.

The large spindle cell of the Walker sarcoma no. 1 is apparently the malignant cell. It has a peculiar large granular nucleus with a distinct nuclear membrane, and during division, which takes place by mitosis, approximately eighty-four chromosomes appear. The mononuclear cell present in the tumor does not differ from that found in other tissues. It divides frequently by mitosis, and the number of chromosomes present at this time is about forty-two, the same as that found in the somatic cells of the normal albino rat.

AUTHORS' SUMMARY.

THE RELATION OF SCABIES TO CARCINOMA. G. AMORMIMO, *Arch. per le sc. med.* **53**:241, 1929.

Rabbits may have scabies due to *Psoroptes cuniculi* Mègnin, which lives in the follicles and in the epidermis. There is produced hyperkeratosis and proliferation of the follicles, but in no case was atypical epithelial proliferation observed. The lesions studied by Borrel in scabies and interpreted by him as carcinomatous are regarded by the author as reactions of a chronic inflammatory nature.

RELATION OF MAMMARY FIBRO-ADENOMATOSIS TO BENIGN AND MALIGNANT TUMORS OF THE BREAST. H. KÜCKENS, *Beitr. z. path. Anat. u. z. allg. Path.* **80**:40, 1928.

A series of 86 surgically removed mammary glands studied by the author contained 12 examples of what he terms idiopathic fibromatosis (Reclus-Schimmelbusch's disease), 8 of fibromatosis with marked epithelial proliferation and 14 of fibromatosis with benign tumors, most of the latter being fibro-adenomas, 1 of fibromatosis with sarcoma and 20 of fibromatosis with carcinoma. In addition to these, for comparative study there were 4 examples of postinflammatory fibrosis, 2 of tuberculous fibrosis, 10 of solitary fibro-adenoma, 13 of primary carcinoma not associated with fibromatosis and 2 of primary sarcoma not associated with fibromatosis. In his preliminary discussion of fibromatosis, the author considers the diffuse and slowly progressing overgrowth of fibrous tissue the primary process which has its origin in part in local factors but to a greater degree in improper functioning of the sex organs, which have a relationship through hormones with the mammary gland. Cyst formation is secondary and is due to occlusion

of ducts by the fibrous tissue. Cyst formation helps to initiate epithelial proliferation. The elastic tissue of the mamma increases progressively with age but bears no relation to the fibromatosis. The benign tumors which may arise either singly or multiply in the breast in which Schimmelbusch's disease is present consist usually of both fibrous and epithelial tissue, either of which may predominate. They arise within the abnormal tissue as the result of factors which lead to localized overgrowth of either tissue element or of both elements. The epithelial proliferation may become so marked as to make it necessary to consider it precancerous. Carcinoma may arise from single or multiple foci of unrestrained epithelial proliferation, in which endocrine factors which originate in the sex organs play a part. The carcinoma may develop in tissue which is the seat of diffuse fibromatosis or in benign fibro-epithelial tumors which have arisen in such tissue. The cancerous epithelium may come from either duct or acinar epithelium. Its growth may be chiefly intraductal, when it may have papillary, glandular or solid character, or it may early penetrate the wall of the duct or acinus and form glandular or solid carcinomatous tissue. The author believes that fibromatosis is so frequently a precursor of carcinoma that suggestive epithelial proliferation should lead to radical operation.

O. T. SCHULTZ.

UNUSUAL TUMORS OF THE MAMMARY GLAND. H. KÜCKENS, *Beitr. z. path. Anat. u. z. allg. Path.* **80**:116, 1928.

A series of surgically removed mammary glands which the author used for a study of the relation of adenofibromatosis to tumor and which is reported in another article (*Beitr. z. path. Anat. u. z. allg. Path.* **80**:40, 1928) contained a number of unusual tumors which the author describes and discusses. There were three examples of epidermoid cyst, which the author says is rare in the breast. The cysts were the size of a bean and were situated in the subcutaneous tissue beneath the nipple. They had no connection with the surface epidermis. They were lined by epidermis, the innermost layers of which were hornified, and they were filled with fatty material that contained granules of calcium. No epidermal derivatives were present in the wall and none were present in the immediately surrounding tissue. The author derives the cysts from misplacements of the embryonic epidermal downgrowths which form the milk ducts. Two carcinomas of the breast, one the size of a pea and the other the size of a small hazelnut, are described because of their minute size. They were embedded in the adipose tissue of the gland and were found only after careful sectioning of the gland. There was no carcinoma elsewhere in either breast, but the mammary tissue was the seat of adenofibromatosis. The author calls attention to the ease with which such small, minute, malignant tumors might be overlooked. A hemorrhagic carcinoma, which was of medullary type, contained cystic cavities filled with old blood and degenerated tumor tissue. The hemorrhage was the result of trauma. In a psammomatous carcinoma of the male breast, the centers of the tumor alveoli were calcified. A carcinosarcoma consisted of glandular carcinoma alveoli embedded in spindle celled sarcomatous tissue, the latter predominating in amount. Metaplasia of carcinoma to sarcoma and intergrowth of two originally distinct tumors are considered as possible explanations, but the author thinks that the tumor arose as a carcinoma, which stimulated the stroma to malignant proliferation. The author claims that the literature contains only twenty cases of carcinosarcoma of the mammary gland; these are briefly reviewed. There was a case of primary carcinoma of the mammary gland in a woman who also had a carcinoma of the uterus; the latter was also considered primary. The author claims that there are only two previously reported cases of primary carcinoma of the mammary gland associated with primary carcinoma of the uterus.

O. T. SCHULTZ.

TUMORS OF THE THYMUS. A. MATRAS and A. PRIESEL, *Beitr. z. path. Anat. u. z. allg. Path.* **80**:270, 1928.

The authors describe in detail seven tumors of the thymus, occurring in persons whose sex and age were respectively as follows: a woman, aged 62; a man,

aged 28; a man, aged 33; a man, aged 56; a woman, aged 52; a woman, aged 60, and a man, aged 35. In two cases the tumor had caused no clinical symptoms, was encapsulated, microscopically was sharply delimited and histologically was benign. These were composed of epithelial reticulum, in which were moderate numbers of lymphocytes, usually most numerous about the blood vessels. A third tumor was purely epithelial in structure and contained no lymphocytes; although well delimited in the gross, it had led to metastasis in a regional lymph node. The remaining neoplasms were clinically and anatomically malignant; they metastasized to the pleura, lung and mediastinal and bronchial lymph nodes. Three of these were so rich in lymphocytes in many areas as to suggest lymphosarcoma. At the periphery, however, the characteristic large cell, epithelial reticulum, was evident. Such lympho-epitheliomatous tumors are the most characteristic ones of the thymus, since they contain both the lymphoid and the epithelial elements of the normal organ. The remaining neoplasm had the histologic appearance of a spindle and large round cell sarcoma. In places these cells were united into a reticulum which established their origin from the epithelium of the thymus. Lymphocytes were not numerous; they were scattered about diffusely, in places separating the cells of the reticulum. In view of the varied morphology which thymic tumors may show, and especially because of the frequent combination of both lymphoid and epithelial elements, they can be called neither sarcomas nor carcinomas. Thymoma might be the better designation. Under this heading three groups can be made: epitheliomatous, the tumors of this type being relatively benign; lympho-epitheliomatous, such tumors being invasive and malignant, and lymphoreticular, the tumors simulating sarcoma and being less malignant than the lympho-epithelial type. No evidence of a transformation of epithelial cells to those of lymphoid type, as has been described by some authors for the normal thymus, could be seen in the tumors studied.

O. T. SCHULTZ.

TUMORS OF THE FIFTH NERVE AND GASSERIAN GANGLION. F. ALTMANN, *Beitr. z. path. Anat. u. z. allg. Path.* 80:361, 1928.

Altmann describes in detail two cases of tumor involving the gasserian ganglion and the trunk of the fifth nerve, one in a man, aged 31, the other in a man, aged 55. In the first case, the clinical diagnosis was tumor, probably osteosarcoma, involving the base of the skull. The neoplasm occupied the middle cerebral fossa of the base of the skull and grew backward into the posterior fossa. It involved both the gasserian ganglion and the trunk of the nerve so extensively that it could not be determined whether it had its origin in the ganglion or in the nerve trunk. In the second case the probable clinical diagnoses were tumor of the brain or cerebellar encephalitis. The tumor had its origin in the sensory portion of the trunk of the left fifth nerve and involved the ganglion secondarily. Its growth was chiefly posterior toward the cerebellopontile angle. The two tumors were histologically much alike and are considered neurinomas. The author pays particular attention to the regressive changes which had occurred and which he considers characteristic of neurinoma. These consist of edematous separation of the tissue elements, which may go on to pseudocyst formation as in the second case and may lead to pleomorphism of the cellular elements; hyalinization, especially of the perivascular fibrous tissue, and interstitial hemorrhage, the areas of hemorrhage undergoing organization and hyalinization. In the first case there was, in addition to these changes, considerable fatty change, which was associated with the formation of pseudoxanthoma cells which had phagocytosed the fatty detritus. Twenty-one previously reported solitary tumors of the gasserian ganglion or fifth nerve trunk are reviewed. Twelve of these were left sided and eight were right sided. Seventeen occurred in males and three in females. The age distribution by decades was as follows: 25 to 35 years, 6; 35 to 45 years, 2; 45 to 56 years, 9. Nine of the tumors are classified as neurinomas or neurofibromas, the author considering them all probably neurinomas, and twelve as neurocytomas. The tumors of the latter group arise within the ganglion itself, may contain newly formed ganglion cells and glia and are clinically and histologically the more

malignant. The neurinomas may arise from the nerve trunk itself, and apparently more often from the sensory than from the motor portion. Their growth is less rapid than that of the neurocytomas. New formation of axis cylinders apparently occurs. As a further contribution to the regressive changes which may occur in the neurinoma, Altmann adds the description of a neurinoma of the left second cervical nerve, which arose in the anterior root and showed the same regressive changes as were noted in tumors of the fifth nerve.

O. T. SCHULTZ.

URINOGENOUS METASTASIS OF RECTAL CARCINOMA. A. BÖGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:640, 1928.

The author reports a case of rectal carcinoma which invaded the ureter of one side at about its middle third. Obstruction of the ureter was not complete, but in the lying position there was some retention of urine in the pelvis of the kidney, without, however, any pyuria. Carcinoma metastases were present on the inner surface of the renal pelvis and in the papillae of the kidney. The author holds that the metastasis is due to carcinoma cells transported upward in the retained urine.

O. T. SCHULTZ.

EXCHANGE OF ELECTROLYTES BETWEEN TUMOR TISSUE AND SOLUTION. G. L. ROHDENBURG and A. BERNHARD, Ztschr. f. Krebsforsch. **28**:301, 1929.

In the experiments of Rohdenburg and Bernhard, small fragments of rat tumors of various kinds and control bits of normal rat liver, skin and other tissues were placed in isotonic electrolyte solutions of varying composition. The latter imitated as closely as possible the blood plasma of rats with growing tumors and of animals with regressing tumors. Variations in exchange between tissue and solution were detected by changes in the weight of the tissue. Tumor tissue tended to lose weight during the first hour and a half of immersion, especially in solutions of the composition of the plasma of rats with regressing tumors. After longer immersion the weight loss became equalized. The tumor tissue gave up sodium to the solution and took up potassium. Tumor tissue gave up a slightly greater amount of nitrogen than did normal tissue.

O. T. SCHULTZ.

NEUTRAL RED AND IODINE REACTIONS OF CANCER SERUMS. B. S. ACEVEDO, Ztschr. f. Krebsforsch. **28**:311, 1929.

The author tried the reaction described by Botelho on 436 serums, and the older neutral red reaction of Roffo on 150 serums. The first consists of the addition to serum of a measured amount of dilute nitric acid in normal physiologic solution of sodium chloride, followed by three successive additions of a solution of iodine in potassium iodide; a positive reaction, said to denote cancer, is indicated by the persistence of the precipitate formed. The formation of precipitate was found to vary with the protein content of the serum, necessitating refractometric determination of serum albumin and globulin. Neither of the reactions tried was found by the author to be specific for tumor. Each gave a fairly high proportion of positive results in the serums of persons free from tumor, and a still higher percentage of negative results in patients with cancer. The reactions depend, not on the presence of tumor, but on hydrogen ion concentration and chemical composition of the serum not necessarily characteristic of cancer.

O. T. SCHULTZ.

PSEUDOMYXOMA PERITONEI OF APPENDICEAL ORIGIN COMBINED WITH PSEUDOMUCINOUS CYST OF OVARY. E. SCHULZE, Ztschr. f. Krebsforsch. **28**:316, 1929.

This is the report of a case of pseudomyxoma of the peritoneum, resulting from perforation of a mucocoele of the appendix. This condition was associated with a pseudomucinous cyst of the ovary, a combination which leads to discussion

of the difficulty of determining the origin of the peritoneal condition when both appendix and ovary are involved.

O. T. SCHULTZ.

EFFECT OF AVITAMINOSIS ON TRANSPLANTABLE MOUSE CARCINOMA. O. THIES, *Ztschr. f. Krebsforsch.* **28**:328, 1929.

Thies reviews the previously published experimental work relating to the effects of quantitative and qualitative food deficiencies to the growth or recession of tumors. The tumor used in his own experiments was a Jensen strain of mouse carcinoma. The mice were kept on a diet deficient in A and B vitamins, which were supplied to the controls in the form of cod liver oil or yeast or both. The state of vitamin deficiency produced had no demonstrable effect on the number of takes or on the growth or regression of the tumor. The period during which the mice were on the deficient diet before being inoculated was short, a fact which the author admits may have had some effects on his results.

O. T. SCHULTZ.

### Medicolegal Pathology

FATAL PHENOBARBITAL POISONING. H. N. WRIGHT, *Arch. Int. Med.* **43**:85, 1929.

It was decided that phenobarbital killed a woman whose body was found in a room in Minneapolis about twenty hours after her death. Chemical quantitative isolation of phenobarbital (luminal) was accomplished in the Department of Pharmacology at the University of Minnesota. The method employed is described and recommended. The statement is made that this is the first death of poisoning from this drug reported, although about twenty nonfatal cases of poisoning have occurred. This seems rather surprising in view of the frequent deaths from the closely related veronal. The report is accompanied by a brief review of the literature.

E. R. LE COUNT.

DIAGNOSIS OF SPECIES BY MICROSCOPIC STUDY OF BONES. C. CANUTO, *Arch. di antrop. crim.* **47**:948, 1927.

Twenty-two small fragments of bone required examination for a medicolegal investigation. The greatest dimension of any one was less than 1 cm. They were fragile and well calcified, and biologic methods in fixing their source were impracticable. By measuring the diameter of the haversian canals in microscopic preparations they were identified as being from a human being. These channels in man have as their smallest diameter one of from 10 to 15 microns, whereas in bones of other animals the diameters are larger; in swine, 40 microns; in rabbits, from 70 to 75 microns, etc. Canuto describes the methods he employed.

E. R. LE COUNT.

EXPERIMENTAL STUDIES OF ALCOHOLIC INTOXICATION. V. M. PALMIERI, *Arch. di antrop. crim.* **48**:477, 1928.

Experimental studies on dogs as to the effect of alcohol on the speed of sedimentation of red blood cells, the nuclear lobulation of leukocytes, the leukocytic ferments and phagocytosis show that, following ingestion of alcohol, there is a decrease in the phagocytic power of the leukocytes, manifested not only by the phagocytic index, but also by the decrease in the percentage of the phagocytic elements. With the ingestion of increasing amounts of alcohol there is a considerable depression of the phagocytic functions. The author concludes that alcoholic intoxication influences the phagocytic power, to a degree parallel with the quantity consumed. The nuclear lobulation of the leukocytes in normal dogs remains more or less constant. Under the influence of alcohol, an alteration of

the normal nuclear appearance takes place, which, however, does not follow any definite rule. The changes are not due to direct action of the alcohol, but are purely functional, accidental and indeterminate. Interesting are the observations regarding the peroxidase reaction, which appears increased during the alcoholic intoxication and achieves its normal level about forty-eight hours after the ingestion of alcohol.

E. L. MILOSLAVICH.

TRAUMA AND LYMPHOGRANULOMATOSIS. A. GERONNE, *Aerztl. Sachverst.-Ztg.* **33**:243, 1928.

This disease was recognized in a man, aged 18, nine months after he was severely injured by an automobile. After being knocked down, he was pinned under the front axle, so that some crushing of the chest occurred. If any of the bones of the thorax were broken, this escaped notice, since the head was also injured and a basal skull fracture suspected. Following the injury there was pain in both sides of the chest intermittently until glandular swelling was noticed, and during some of this period the sputum was bloody. In concluding that the accident had provoked the disease already latent to developing more rapidly than it would have without the injury, the following were important: that no other cause for the disease except the accident was obvious, and that the chain of symptoms between the injury and the disease was established, a thorough examination three months before the accident revealing only slight color blindness. Shortly after this expert opinion was given, the diagnosis of lymphogranulomatosis was confirmed by postmortem examination.

E. R. LE COUNT.

ACCIDENT, SUDDEN DEATH AND SYPHILITIC LEPTOMENINGITIS. W. WEIMANN, *Aerztl. Sachverst.-Ztg.* **33**:335, 1928.

While lifting a heavy drum (150 Kg.) on which wire was to be wound, two men fell but sustained no injury; the affair was not looked on as an accident, and the men finished their day's work. When one of them arrived home, he complained of abdominal pain and remained home the next day. On the third day, he went to a hospital but died on his arrival. The postmortem examination disclosed a generalized syphilitic leptomeningitis, markedly basilar, an intrapontile hemorrhage extending into the left cerebral peduncle and the entire brain stem as edematous. There were also aggregations of lymphocytes in the suprarenal cortices interpreted as syphilitic disease; the aorta was normal grossly. In reviewing the possibility of a connection between lifting the heavy drum and the hemorrhage and their bearing on compensation, it was decided that the occurrence in the factory had no relation to the sudden death, that the stomach ache was from chronic gastritis and that the hemorrhage would have been evident much sooner if caused by the strain of lifting or the fall. Many of the blood vessels in the leptomeninges, involved from without by the inflammation, were occluded by thrombi, some older than others. Death from spontaneous intracerebral hemorrhage without any preliminary coma is rare; but unexpected death from syphilis of the brain is observed more frequently.

E. R. LE COUNT.

GARAGE DEATHS. O. MARIENFELD, *Aerztl. Sachverst.-Ztg.* **34**:15, 1928.

This general review for physicians officially engaged in legal work and in insurance emphasizes the importance of investigating the garage and its equipment, the exact state of affairs in such places when persons are found dead in them, the open or closed doors and windows, ventilation, gas heating, electric wiring, temperature and other conditions of the machinery of the motor vehicles, the place where the body was found, just how the trunk and extremities lay, etc. The odors and smokiness of the vapors are also important and should be noted, if possible, before windows and doors are opened for airing. During 1926, the deaths in garages in Prussia numbered 242. Such deaths are not all from carbon monoxide. Some

are from benzine or benzol poisoning; others are electrocutions or from natural causes; many are accidental and some suicidal. Apparently, as yet, no considerable number have been homicidal.

Accompanying the exposition of such matters are many valuable suggestions regarding the postmortem examination of bodies of persons found dead in garages, although no attempt is made to present the pathologic anatomy of carbon monoxide, or of other, poisonings extensively. Public and private legal rights and details of liability for insurance and of the legal exemption for liability are also discussed. A number of references to unusual observations are included, some of them to hemorrhages and softening of the brain from carbon monoxide poisoning, and, according to the reports, with much less of an interval between poisoning and death than has been noted by most authorities.

E. R. LE COUNT.

LATE HEMORRHAGE WITH TRAUMATIC RUPTURE OF THE SPLEEN. P. KLASSEN, Aerztl. Sachverst.-Ztg. **34**:145, 1928.

Allusion is made with citations to reports by different writers of altogether fifteen deaths from intraperitoneal hemorrhage following traumatic rupture of the spleen, the intervals between injury and death being from one and a half to twelve days. The interval in Klassen's case, the sixteenth, was seven days; the injury was a blow from a piece of bread thrown by the wife of the patient. The external violence in these delayed bleedings is often slight, as this one was, and may attract no attention. In fact, questioning at great length may be required in learning of an injury. The tears are subcapsular for the interval, and the final break through the capsule into the abdominal cavity may be due to any one of a number of exertions, such as occur with lifting, coughing, vomiting, etc., by which the spleen is compressed by the diaphragm and wall of the trunk. With the stomach full, the concave surface of the spleen is supported and blows driving in the tenth rib, which has its long axis parallel with that of the spleen, tear the outer convex surface. With the stomach empty, the poles of the spleen are disposed to bend out, stretching the concave surface, so that the tears are in or just beneath the capsule about the splenic hilum. These late hemorrhages are especially important from the point of view of industrial insurance and of claims by laborers for compensation; for, after the violence, persons have been known to walk a mile without complaint; to walk home, then to a physician and finally to a hospital; to walk upstairs; to ride a bicycle or to carry burdens. A common symptom is pain in the left shoulder and left side of the thorax.

E. R. LE COUNT.

DEATH IN A "BLEEDER" FROM OCCUPATIONAL STRAIN. P. KISSINGER, Aerztl. Sachverst.-Ztg. **34**:319, 1928.

The symptoms of weakness came on suddenly while the man in question was lifting cement blocks. He was 45 years old, and was known as a "bleeder," having had severe hemorrhages from simple cuts on his fingers, extraction of teeth, etc. He entered the hospital four days after his attack, complaining of weakness and tenderness in the right lower quadrant of the abdomen, where there was a swelling as large as a fist. He knew his condition and diagnosed his trouble. Since the accident he had become anemic; he died eighteen hours after entrance. A huge hemorrhage was found in the right iliac fossa retroperitoneal extending up so as to surround the right kidney. Its source was not found. Others have reported similar accidents in persons with hemophilia: one was a fatal intestinal hemorrhage in a man who had pressed with his abdomen on a lever; a second was a death from renal hemorrhage following a severe strain, and a third was a huge fatal hemorrhage in an obese bank official about the urinary bladder and adjacent structures, brought on by coughing.

E. R. LE COUNT.

INFECTION WITH SYPHILIS FROM POSTMORTEM EXAMINATIONS. P. MGAL-OBLISCHWILI, *Dermat. Ztschr.* **51**:167, 1927.

Among the conclusions of the author, these occur: The impression that syphilis cannot be contracted in working with cadavers is wrong; it may be contracted from bodies more than twenty-four hours dead; by making inquiries of directors of pathologic institutes, twenty well established cases were found, and fourteen that were probable; the chancre was on the digits in all but one of those cases, in which its location was learned, the exception being a case in which it was on the neck; in three persons so infected, the syphilis was malignant; errors in diagnosis were frequent; the greatest danger is in the bodies of infants and children with congenital syphilis.

E. R. LE COUNT.

CENTRAL TRAUMATIC HEMORRHAGE OF THE BRAIN. RENTER, *Deutsche Ztschr. f. klin. Chir.* **207**:92, 1928.

Deeply placed hemorrhages in such places as the internal capsule lenticular nuclei, pons or optic thalami may be caused by relatively slight violence. They may constitute the much disputed "late traumatic apoplexy." Caution is necessary in deciding whether apoplectic strokes coming on several weeks or months after a severe injury of the head are from spontaneous or from traumatic hemorrhage. When they occur after six months or later, they are probably due to trauma. Seven cases are reported.

E. R. LE COUNT.

IDENTIFICATION FROM REMNANTS OF SKELETONS. NIPPE, *Med. Welt.* **1**:1551, 1927.

An unknown man who killed himself was identified by the dental work he had received. Through the peculiarities of a second skull, indicating a mixture of the Slav and Tartar races, it was identified as that of a Russian prisoner of war who had disappeared. This led to the discovery that he had been murdered by his wife and a stepson, who were then executed. Another skull was identified as that of a soldier who had killed himself, by the evidence of an operation in the left frontal region. A fourth identification was made from the changes in the head of a right humerus, which indicated an extreme limitation of movement. This also resulted in the disclosure of a murder.

E. R. LE COUNT.

INDUSTRIAL INJURIES OF THE EYE. FUCHS, *Wien. med. Wchnschr.* **39**:1220, 1926.

According to statistics from different sources, from 20 to 38 per cent of blindness results from accidents. Of industrial accidents requiring compensation, injuries of the eye make up about 8 per cent. Those least dangerous are from carbon or metallic particles small enough to float in, or be blown about in, the air and to lodge in the eyes. The larger splinters of metal which are driven into the eyes from machinery cause more serious wounds. Among 1,000 workers in metals, 28 suffer some damage of vision and 16 lose one eye, according to some of the records. An infection of a nonpenetrating wound may cause the loss of an eye, and when fragments of metal become embedded in the eyeball without subsequent infection, blindness ultimately results without their removal.

E. R. LE COUNT.

THALLIUM POISONING F. REDLICH, *Wien. klin. Wchnschr.* **40**:694, 1927.

With the intention of committing suicide, a young woman took a quantity of rat poison sold under the trade name of "Celio," or "Zelio," which contains 10 per cent of thallium sulphate. She suffered from intense pain in the legs, abdominal colic, vomiting and hyperalgesia and hyperesthesia of the legs. Sugar and albumin appeared in the urine. There was a lymphocytosis and three weeks



later the hair of the scalp came out in large masses. Previously, multiple neuritis and achylia have also been noted. Children are less susceptible than adults to thallium.

E. R. LE COUNT.

OCCUPATIONAL ANTHRAX. REBENTISCH, Zentralbl. f. Gewerbehyg. **3**:162, 1926.

It was learned from insurance officials that during twenty years 648 laborers in the leather industries in Germany acquired anthrax and 98 died from the infection. The average number of persons employed each year was 37,274. The pustules in 93.2 per cent of the cases were on the exposed parts of the head, neck, arms or hands. The diagnosis was properly established in 95.7 per cent of the cases. Only 3.1 per cent of the infected skins were domestic.

E. R. LE COUNT.

ACCIDENTAL WOUNDS AND OTHER INJURIES OF BURSAS. J. J. WEHRLI, Inaug. Diss., Zurich, 1927.

Using the available information gathered for insurance records in Lucerne, beginning with 1923, the author found that 56.32 per cent of 522 cases of acute bursitis followed single injuries of considerable violence; in 25.67 per cent, the inflammation was purulent; in 83.8 per cent, healing took place in four weeks; in 8.9 per cent, healing was not complete at the end of two months, these all being purulent; 21.4 per cent of the cases were not concerned with occupations or industry; there were recurrences in 7.6 per cent; in 12.4 per cent, labor was not interrupted; in 55.17 per cent bursitis was of the knee, and in 42.9 per cent of the elbow. In only 6.51 per cent was the trouble caused by repeated trivial irritation, and chronic. These were practically all housemaid's knee.

E. R. LE COUNT.

NECROSIS OF THE HEART FROM RADIUM. WEGELIN, Schweiz. med. Wchnschr. **8**:895, 1926.

Two patients died suddenly from intrapericardial hemorrhage caused by necrosis of the heart wall and rupture, this, in its turn, being caused by radium treatment for esophageal cancer. In one, the radium bromide was in the esophagus seventy-two, in the other seventy-four, hours.

E. R. LE COUNT.

## Technical

THE WATER CONTENT OF BLOOD SERUM. HARVEY SPENCER, Am. J. Dis. Child. **37**:546, 1929.

The falling drop method is the most accurate of the several methods compared for measuring the water content in determining the specific gravity of the blood serum. The blood serum of patients exhibiting clinically the most marked dehydration had a higher specific gravity, a greater total solid content and a larger percentage of serum protein than the specimens from normal patients. The falling drop method of determining specific gravity is a procedure of clinical value, owing to its simplicity, accuracy and rapidity.

AUTHOR'S SUMMARY.

CULTURE MEDIA FROM COMMERCIAL DRIED YEAST. JAMES M. NEILL, JOHN Y. SUGG, LURLINE V. RICHARDSON and WILLIAM L. FLEMING, J. Bact. **17**:329, 1929.

This paper describes the method of preparation of culture mediums from commercial dried yeast, and reviews their advantages and limitations. The "5 per cent yeast" broth and agar have been found satisfactory for all routine purposes for which meat infusion peptone mediums are commonly employed. The yeast

mediums are easy to prepare and possess the definite advantages of uniform reliability and low cost (9 cents per liter of broth). Their use is especially recommended for the routine culture of infectious material in clinical bacteriologic laboratories.

## AUTHORS' SUMMARY.

AN IMPROVED METHOD OF CULTURE FROM A SINGLE BACTERIAL CELL. SYDNEY G. PAINE and J. C. RAMCHANDANI, *J. Bact.* **17**:377, 1929.

The method is a modification of the one given in an earlier number of the *Journal of Bacteriology* (Paine, 1927). Attenuations from the culture are made in five sterile watch glasses, as in the method of Paine, but, in place of sterile water, use is made of a sterile solution of nigrosine, as in the method of Burri. With the precautions described in the earlier paper, the appropriate dilutions are taken up with a steel mapping-pen, instead of being spotted on the surface of agar in a dish, are drawn in lines on the surface of a film of agar previously prepared on a long, narrow coverslip. In order to prevent ploughing up the surface of the agar, the steel pen is attached to its holder by a short coil of spring-brass wire. In this way, sufficient rigidity for the control of the pen's direction can be retained while allowing only the slightest pressure of the point of the pen on the surface of the agar. The coverslip is mounted above a glass slide, film side down, conveniently supported at the ends on thin strips of cardboard in such a way that contact of the agar film with the glass slide is just prevented. The ink lines are examined under the 12th inch objective, and the positions of what appear to be single bacterial cells are marked down by spots of Chinese ink. The slides are then placed in a moist chamber and incubated over night. Any colonies that develop at the marked spots from single cells will be of approximately the same size and may safely be assumed to be pure, while any that develop into larger than minimal size may be discarded as impure.

THE VALUE OF VEGETABLE EXTRACTS IN CULTURE MEDIUMS. LUTHER THOMPSON, *J. Bact.* **17**:379, 1929.

Aqueous extracts of potato, carrot, spinach, radish and beef heart were sterilized by filtration and added to nutrient broth aseptically. It was found that as little as 0.01 cc. of these extracts, when added to from 6 to 7 cc. of nutrient broth, would promote growth of many streptococci which did not grow in the broth alone, while 0.2 cc. was sufficient to give vigorous growth of most streptococci. Potato extract was found to be the most satisfactory because of its high nutritive value and because it keeps well without change in reaction or in precipitation of protein. Heat was found to have an effect on the extract proportional to the precipitation, those mediums giving the most precipitate being the least useful in accelerating growth. Both the proteid and nonproteid nitrogen fractions of the potato extract serve to stimulate growth of streptococci, but not in as marked a degree as the whole extract. Potato extract may be used in place of fresh blood in many instances in which it is not essential to observe hemolysis. It is helpful in getting a growth of streptococci and pneumococci free from cells and precipitated fractions of medium. As an enriching substance in ordinary fermentation tubes, it allows growth of streptococci without interfering with the action on the sugar. The substance in potato extract responsible for promoting growth is thought to be nitrogenous material, which furnishes suitable food for the bacteria, rather than food-accessory substances.

## AUTHOR'S SUMMARY.

A NEW HISTOCHEMICAL METHOD FOR ARSPHENAMINE AND RELATED ARSENO-BENZOL DERIVATIVES. N. VON JANCsó, JR., *Ztschr. f. d. ges. exper. Med.* **61**:63, 1928.

Tissues are fixed in solutions of formaldehyde (1 part of 40 per cent formaldehyde solution and 4 parts of distilled water) for from one to four days. Frozen sections are placed either in distilled water or in a freshly prepared silver bath

(to 1.5 per cent aqueous solution of silver nitrate, ammonium hydroxide is added, drop by drop, until the precipitate redissolves; to the clear solution an equal amount of purest glycerin is added). The sections are placed in this bath for from thirty to fifty-five minutes, care being taken to prevent their sticking together; the bath should be gently shaken. The sections are then washed in distilled water for about one minute and placed in a 1 per cent aqueous solution of sodium thiosulphate for from three to ten minutes; they are now transferred again to distilled water, dehydrated in the usual manner, washed in xylene and embedded in balsam. Arspenamine and other arsenobenzol derivatives appear as brown or black granules. The method may be combined with nuclear staining (hematoxylin, alum carmine), staining for fats, etc. If minimal quantities of arspenamine are to be demonstrated (as in human tissues after ordinary intravenous medication), it is advisable to place the sections for one hour in pure glycerin after the silver bath. (For further technical details the original paper and the author's previous publications, cited in the text, should be consulted.)

By means of this histochemical method, it has been possible to study the localization of arspenamine and related preparations in the various tissues of man and animals. The author has shown that certain arsenobenzols are stored by the reticulo-endothelial cells. There were considerable and characteristic differences in the distribution of nine different forms of arsenobenzol derivatives. In general, these substances are distributed and stored like the acid vital dyes, such as benzopurpurin.

BALDUIN LUCKE.

THE DIAGNOSIS OF ENDOCARDITIS LENTA. H. KÜRTEEN, *Ztschr. f. d. ges. exper. Med.* **61**:494, 1928.

A characteristic serum reaction in fifty-five cases of endocarditis lenta is described. To 1 cc. of serum in a test tube are added 2 drops of 40 per cent neutral solution of formaldehyde; the tube is shaken to produce thorough mixing, and is then allowed to stand at room temperature. During the next two hours, the presence or absence of gelation is noted by tilting the test tube. Kürten has examined the serums of over 1,100 patients and healthy persons by this test. Normal serums remain liquid for twenty-four hours; the serums from thirty-five cases of endocarditis lenta gelled either immediately or within two hours after the addition of solution of formaldehyde. The serums of five patients not suffering from endocarditis lenta (two with nephrosis, two with uremia and one with amyloid disease) gave a positive reaction. The author demonstrated that the reaction depends on an increase of the globulin fraction of the blood. While not specific, the reaction with solution of formaldehyde is of diagnostic value in cases of endocarditis lenta; other forms of endocarditis give a negative reaction.

BALDUIN LUCKE.

A NEW HISTOCHEMICAL METHOD FOR ARSPHENAMINE AND RELATED ARSENOBENZOL DERIVATIVES. JOSEPH SCHUMACHER, *Ztschr. f. d. ges. exper. Med.* **63**:804, 1928.

Schumacher calls attention to his publications on the demonstration of arspenamine, which are not mentioned in the article by von Jancsó. References are given to his work. This is of interest in connection with the paper by von Jancsó abstracted in the ARCHIVES.

BALDUIN LUCKE.

# Society Transactions

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## NEW YORK PATHOLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE

*Joint Meeting, May 2, 1929*

HARRISON S. MARTLAND, *Presiding*

### NEW METHODS FOR THE SERODIAGNOSIS OF SYPHILIS. ERNST MEINICKE.

I shall say a few words about the old and new theories of the Wassermann reaction and the flocculation tests. The modern view of Sachs that there is a reaction between lipoids and antibodies against lipoids is at the bottom of all the reactions. The hypothesis of Klopstock is that the principle of the methods is an immunity reaction against the spirochetes and at the same time (combining his hypothesis with that of Sachs) an immunity reaction against lipoids. The new theories may be right, but they are not yet sufficiently proved. Nevertheless, the serodiagnostic methods have an ever-increasing practical importance in the detection of cases of syphilis and as a guide in treatment.

Until 1917, none of the flocculation reactions had practical importance. My Kochsalzmethode (sodium chloride method, M. R.) was the first which was proved to be of practical value. In 1918, Sachs and Klopstock followed with their reaction. In 1918, I published a second one, introduced in the literature as D. M. In 1921, Dold published the first turbidity test as a rapid test. I applied his theories to my own reaction and described my turbidity test, which as M. T. R. has extended widely throughout the world. New progress was made by Kahn and Muller. Both described reactions which were more sensitive than the old ones, and at the same time at least as specific. The International Serological Conference of last year at Copenhagen proved beyond doubt that both methods are more apt to fulfil the purpose of detecting cases of syphilis than the old methods. The Muller reaction is rather difficult to perform; the Kahn test, on the other hand, is not so difficult to set up, but there can sometimes arise some doubt in the reading of the results.

I therefore tried to develop and improve my turbidity test and to find a reaction as sensitive as possible and at the same time easy to perform and read. As a result of my investigations I published a reaction, called the Meinicke-Klärungs-Reaktion (M. K. R.) clarification reaction. The principle of this method is the clearing up of the mixture of serum and extract dilution, formerly opaque and milky turbid. The extracts used in this test are the same as in the M. T. R., only the amount of balsam of Tolu has been increased. (An exact description of the preparation of the antigen will be published in detail.) A short description of the performance of the test and the reading of the results was given.

The new test has been worked out lately (publication in print) as a rapid test and as a microreaction. In this form it is a flocculation reaction and not a clarification reaction. The principle is the formation of conglomerations in the positive cases, which can be easily observed through a microscope, using a small magnification of about 60 times. A short description of the performance of the micro test and of the readings was given.

In comparison with the Kahn test, the Wassermann test and the M. T. R. (turbidity test) with this new one in 3,000 cases, it has been shown that the Kahn test and the M. K. R. form one group of reactions which is much more sensitive than the Wassermann test and the M. T. R. There is a high percentage of positive cases in favor of the Kahn test and my new method. According to my experiences the clarification reaction is even more sensitive than the Kahn

reaction. In some positive cases it gives a positive result, whereas the Kahn test is negative or only weakly positive. The opposite occurrence is rather seldom. As at Copenhagen there are some exceptional cases, in which the old weak methods are superior to the new ones. Concerning the specificity, the new methods are more trustworthy than the old ones.

There can be no doubt that a sensitive method is of the highest value in detecting cases of syphilis. On the other hand, it must yet be proved whether the sensitive methods are not perhaps too strong to be a good guide during the treatment.

I venture to think it would be of great value to the scientists in this country in which the Kahn test is rather widespread to have now in my clarification reaction a simple method with which to check the Kahn test. In view of this I want to introduce my new tests into this country, and should be pleased to have them given a trial.

#### DISCUSSION

JOHN A. KOLMER, Philadelphia: It is highly probable, as Dr. Meinicke has indicated, that the antibody-like substance responsible for the complement-fixation reaction in syphilis is identical with that which causes the numerous flocculation reactions. It is also rather unfortunate that so much confusion has been developed in the serology of syphilis, particularly from the standpoint of the practitioner. Since Wassermann described his test in 1905, there have been developed a large number of modifications of his test, that usually bear his name, but many of these are indeed different, both in principle and practice, from the original Wassermann reaction, and many of the flocculation tests which have been developed since 1907 have been compared with the so-called Wassermann reaction without much attention being paid to the technic of the latter.

If one were to compare several of these flocculation reactions as described by Meinicke, Sachs, Dreyer, Kahn and others with the original Wassermann technic, it would be found that they are more sensitive and possibly a bit more specific, but one must compare these flocculation reactions with some of the newer and better complement-fixation tests for this disease. Furthermore, it is far more important to estimate the value of these flocculation reactions in relation to the diagnosis and treatment of syphilis than it is merely to compare them to the Wassermann reaction.

It is not true that these flocculation reactions are simple. They still have to be done by experienced serologists for acceptable results. It has been rather unfortunate that the literature on flocculation reactions has given a widespread impression that these are tests so simple that they can be done in the corner laboratory of the average physician's office. This is not true. These extracts have to be prepared with a great deal of skill, and the tests have to be conducted for the best results by experienced serologists.

We are not so much interested in how the flocculation reactions compare with the Wassermann reaction. We are far more interested in whether or not they improve the status of the serum diagnosis of this disease and as a control on its specific treatment. I think that the consensus in many circles is that none of the flocculation reactions have displaced the better of the complement-fixation reactions. This was the conclusion reached last May at Copenhagen in the Second Laboratory Conference of the Health Organization of the League of Nations to which Dr. Meinicke referred. It would appear that the consensus is that the complement-fixation test should be maintained, and that one or more of the flocculation reactions should be used as an additional test and as a control.

This is my own conclusion. My experience during the last few years has been based on the Kahn reaction, and I have not used the new Meinicke test. I did use his third method prior to 1923, and found that it agreed with the Wassermann reaction in about 90 per cent of cases. I have not had experience with the new modification that he has described this evening, but I find that the Kahn reaction agrees with my new complement-fixation test for syphilis in 96 per cent

of serums and that the difference of 4 per cent is made up of cases in which the patients react positively with the Kahn and negatively with the complement-fixation, or the reverse, with the general tendency for the Kahn reaction to remain positive longer in cases in which the patients were treated than the complement-fixation reaction.

The great difficulty with the flocculation test has been the reading and the interpretation of the weakly positive reactions, as estimated by Dr. Meinicke. It concerns a group of cases that are exceedingly important, because the cases are usually of so-called latent or concealed syphilis, or cases in which the patients have been treated and in which there is but a small amount of antibody in the blood. We want tests for the serologic diagnosis of syphilis that will clear up the doubt that usually surrounds the weakly positive reactions, and I must declare, so far as my own experience is concerned, that for the average serologist, the complement-fixation reaction is easier to read and much less likely to error of interpretation than are the weakly positive flocculation reactions. Furthermore, it has been my experience that the Kahn and other flocculation reactions do not ordinarily fare as well in the small laboratory with the average laboratory technician as does the complement-fixation reaction. If I can judge from the number of cases that are sent to me to untangle from the diagnostic standpoint, and more especially cases in which the diagnosis of syphilis has been made on the basis of a weakly positive Kahn reaction, I rather suspect that there are a good number of false positive reactions being recorded, so that I still believe that a good complement-fixation reaction is superior in the hands of the average laboratory technician than are several of the flocculation reactions. I have learned to view with some skepticism the significance of a weakly positive Kahn reaction, particularly those that give a  $-1$ , or a  $-11$ , because of the frequency with which they may occur in persons in whom syphilis can be excluded clinically. Of course the stronger reactions are just as specific as is the complement-fixation reaction.

Now, as far as a comparison of the Kahn with the complement-fixation test goes, these are best made when serums are carefully collected from groups of patients and tested in the laboratory without the serologist knowing anything about their source. One of the best studies in this connection was conducted in 1926 by Dr. Gilbert and Miss Langworthy, who sent serums to several different laboratories throughout the country, including my own in Philadelphia. In this group of 252 specimens from 227 patients, there were 24 cases of primary syphilis; 58 per cent gave a positive Kahn and 67 per cent gave a positive Kolmer complement-fixation. There were 6 cases of secondary syphilis, and both the Kahn and the complement-fixation reactions were positive in all of them. There were 24 cases of tertiary syphilis; 51 per cent gave a positive Kahn and 71 per cent a positive complement-fixation reaction. There were 21 cases of neurosyphilis; 70 per cent gave a positive Kahn and 80 per cent a positive complement-fixation. There were 30 cases of congenital syphilis; 37 per cent gave a positive Kahn and 40 per cent a positive complement-fixation. There were 105 cases of syphilis in which the patients were treated; 47 per cent gave a positive Kahn and 45 per cent a positive complement-fixation. These results are in line with our general experience in Philadelphia that the complement-fixation test is not really less sensitive. It is equally sensitive, and the two tests conducted together give the best information for the serum diagnosis of syphilis. In my opinion it is not a question of choosing one or the other. It is rather a realization that the serum diagnosis of syphilis is best served by choosing a good precipitation test in conjunction with a good complement-fixation test.

At this Second Laboratory Conference, held last May in Copenhagen, which I regret I was unable to attend because of my work at the University, there were 944 cases studied; 502 were syphilitic, 7 were doubtful and 435 were regarded as nonsyphilitic. Seven different complement-fixation tests were used, and about an equal number of flocculation tests, including the Meinicke test. In the complement-fixation tests, taking the Harrison technic for comparison, in 502 cases of syphilis, there were 58 per cent positive complement-fixation reactions,

including doubtfully positive reactions. In this group Meinicke reported about 56.5 per cent positive reactions. I do not know whether he used the method he talked about this evening or his former method, but his 56.5 per cent corresponded closely to the Harrison 58 per cent. The Kahn test came out much better, giving 67.5 per cent positive reactions. Sachs observed about 55.2 per cent positive reactions. Dreyer reported about 66.3 per cent positive reactions. Vernes, doing his rather complicated test, had 52.1 per cent positive reactions. It is equally important, however, to examine the percentage of positive reactions in cases in which the reaction was regarded as negative. Harrison, with the complement-fixation test, had about 2.7 per cent false positive reactions. Meinicke had 5 per cent false positive reactions; Kahn, 1.1 per cent; Sachs, 0.2 per cent; Dreyer (sigma test), 9.4 per cent, and Vernes had 10.5 per cent. Personally I am opposed to any test that yields falsely positive reactions. Every serologist knows that it is possible to make serologic technic hypersensitive and increase the percentage of positive reactions in syphilis, but that we immediately run the risk of getting false positive reactions in normal persons. I had far rather miss an occasional case of syphilis than to fasten the diagnosis of syphilis on a single nonsyphilitic person. When I devised my own modified complement-fixation test, I adjusted the hemolytic system in such a way that I felt reasonably sure we would miss an occasional case of so-called latent or concealed syphilis, but I had far rather do that than run the risk of getting false positive reactions in nonsyphilitic persons.

In conclusion, I may summarize one or two of the conclusions of this Second Laboratory Conference at Copenhagen, at which it was stated that "it desired to emphasize the fact that, no less than the complement-fixation tests, these flocculation methods are, despite their apparent simplicity, extremely sensitive to slight differences in experimental conditions and subject to so many sources of error, in connection both with the execution of the tests and in the reading and interpretation of results, that they must be placed only in the hands of specially trained serologists."

The Conference being of the opinion that some serologic tests may have the advantage of greater sensitiveness without being absolutely specific and vice versa, and that concordance of reaction of two or more tests has greater diagnostic value than has a single reaction "recommended that, in order to secure the most reliable information to the clinician, at least two different serologic diagnostic methods should be used." The Conference having in mind the necessity for constantly readjusting serodiagnostic methods in order to obtain the highest degree of specificity "recommended that the serologist should check the accuracy of his tests by regular and very frequent reference to the clinical data, in consultation with the clinician, whose assistance in supplying adequate information as to the history of syphilis and the clinical particulars of the case is of great value for the interpretation of the results." The Conference "wished to reiterate with particular emphasis that in spite of the increased sensitiveness which the various serodiagnostic methods have shown at the present Conference, serological results may, notwithstanding the presence of a syphilitic infection, be negative in certain cases; that a positive reaction in the absence of a clear history or of signs of syphilis should, if only to exclude all possibility of error, never be accepted until a test of at least one more specimen has afforded the same result; that except in the case of a few well defined pathological conditions, syphilis is indicated with a degree of probability which closely approximates its certainty when several tests performed according to different methods give a positive result."

As far as my own experience is concerned in serology and likewise in clinical syphilology, I believe that there is still a great need for the complement-fixation test. It is true there are certain times, particularly on board ships, when the complement-fixation test cannot be used, but otherwise the conduct of a complement-fixation test of acceptable accuracy and sensitiveness along with an acceptable flocculation test as a control would appear to serve best the serum diagnosis of syphilis.

ERNST MEINICKE: I may say that it was my old method I used at the last Conference in Copenhagen, and it was there that the tests of Kahn and Muller showed me it was possible to improve the method I had developed. The experience at the Conference was contrary to all opinions we had before. It was proved there that the most sensitive reactions, namely, the Kahn and the Muller tests, were the best concerning the specificity, and the Wassermann test in its several modifications came out well in the rear on account of the specificity. I am a bit skeptical, and we all were at the Conference, of the possibility of strengthening the Wassermann test or one of its modifications, in such a way that it can compete with the new tests, for at Copenhagen the Wassermann test had been worked out not only with inactive serum, but also with active serum, and it is known that a Wassermann reaction set up with active serum is much more sensitive than with inactive serum. I may state that it was the intention at Copenhagen to throw the Wassermann test out and to rely on the flocculation tests. The conclusion Dr. Kolmer referred to was not universal but the majority of the members voted that we ought to keep the Wassermann to check up with the flocculation tests. Some of the members of the Conference, however, were already in favor of the flocculation tests and against keeping the Wassermann test, and it was the impression at the Conference that, though the time had not come for discarding the Wassermann test, the probability was that we could do so, perhaps at the next Conference.

THE FUNCTIONS OF THE GALLBLADDER AND SOME OF THEIR DISTURBANCES  
IN THE LIGHT OF RECENT INVESTIGATIONS. BÉLA HALPERT.

The view most widely accepted regards the gallbladder as a reservoir, the function of which is to supply concentrated bile whenever there is call for such in the intestine. According to another view, of more recent conception, the bile enters the gallbladder not to be stored there and in time expelled, but to be resorbed in toto by the mucosa of the gallbladder (Sweet [Internat. Clinics **1**: 187, 1924], Halpert [Med. Klin. **20**:408, 1924], Blond [Arch. f. klin. Chir. **149**: 662, 1928]). Thus the gallbladder performs at least two main functions: first the return of important constituents of the bile into the circulation, and second by the resorption of bile, the relief and regulation of the pressure within the biliary system while the sphincter of the ductus choledochus is closed (Anat. Rec. **29**:359, 1925). There is considerable evidence, morphologic (Bull. Johns Hopkins Hosp. **40**:390, and **41**:77, 1927) and experimental, supporting this conception.

The first fold of Heister is a high thin semilunar membrane which narrows the lumen at the neck of the gallbladder to less than a third of the original diameter. The orifice is eccentrically situated. At the lower limb of the S-shaped turn of the neck of the gallbladder a second fold narrows the lumen. Here the neck continues into the cystic duct which tapers gradually toward its junction with the common hepatic duct. The crescent-like folds protruding into the lumen of the cystic duct are apparently arranged in a fashion to act as a system of "one way valves": they permit the inflow but prevent or hinder the outflow of bile from the gallbladder.

Data thus far obtained by studying the spontaneous contractions of the isolated gallbladder of the dog (Anat. Rec. **42**:50; 1929) indicate that the function of the muscular coat is that of preventing overdilatation and to affect adjustment in size to the varying content. It was found that when the fluid content of the isolated gallbladder suspended in an oxygenated bath of Locke's solution at body temperature, was raised or lowered, a change was registered, but soon adjustment occurred and the curve returned to the previous level and resumed its former shape.

Experiments with methylene blue on the rabbit (Am. J. Physiol. **88**:351, 1927) prove beyond doubt that at least in this animal, and also in the rhesus monkey, when bile leaves the gallbladder through the cystic duct, this is rather an excep-



tion than the rule. These experiments also throw some light on the mechanism of the formation of gallstones. Abnormal composition of the bile or a disturbed resorptive function of the gallbladder mucosa leads to stagnation of bile in the biliary vesicle.

If stasis of stone-forming constituents in the gallbladder is due to an increased excretion of these elements or to a disturbed or altered functioning of the liver, we may speak of a "hepatogenous" stasis in the gallbladder. Experiments with methylene blue furnish a striking example of such a hepatogenous stasis (ARCH. PATH. 7:473 [March] 1929). Injected intravenously or given by mouth, methylene blue appears in the bile and is poured into the gallbladder; the mucosa of the latter apparently cannot resorb the dye fast enough to cause its rapid disappearance, and so the dye stays there for days. It is evident that much the same thing happens when the sodium salt of tetraiodophenolphthalein is administered for cholecystography. Both of these examples of hepatogenous stasis in the gallbladder support the idea that something of the same order happens in cases of marked cholesterolemia, when the cholesterol content of the bile is correspondingly exaggerated.

If the stasis in the gallbladder is caused by intrinsic functional disturbances or demonstrable pathologic conditions of the gallbladder itself, with the functioning of the liver more or less unimpaired, one may speak of a "cystogenous" stasis in the gallbladder.

Perhaps the most convincing evidence for the existence of these two types, the hepatogenous and the cystogenous stasis, is furnished by the concretions usually found in these conditions.

The chemical composition and the architecture of gallstones permit their ready classification into three groups (ARCH. PATH. 6:623 [Oct.] 1928). Those consisting purely or mainly of one of the stone-forming constituents of the bile, such as (a) cholesterol, (b) biliary pigments (calcium bilirubinate) and (c) calcium carbonate may be classed as group 1, i. e., the group of "pure gallstones." For the formation of all of these so-called "pure gallstones," the liver rather than the gallbladder may be considered primarily responsible. Group 2 is the group of "mixed gallstones," that is, those consisting purely or mainly of at least two of the constituents of the "pure gallstones." Their formation has generally been associated with infection. Infection and inflammation damage the mucosa of the gallbladder so that not all of the constituents of the bile are resorbed. Thus "mixed gallstones" are formed in cystogenous stasis in the gallbladder, the stagnation being responsible for the formation of the stones and the infection for the stagnation.

When a hepatogenous stasis in the gallbladder which has led to the formation of pure gallstones, precedes a cystogenous stasis, "combined gallstones" form, which have a nucleus formed by one of the members of the group of "pure gallstones" and have a shell formed by one of the members of the group of "mixed gallstones." If, on the other hand, a cystogenous stasis in the gallbladder which has led to the formation of mixed gallstones is followed by a hepatogenous stasis, "combined gallstones" form which have a nucleus formed by one of the members of the group of "mixed gallstones" and have a shell formed by one of the members of the group of "pure gallstones."

#### DISCUSSION

B. P. BABKIN, Montreal: Dr. Halpert emphasizes one of the functions of the gallbladder, and nobody, of course, denies this function. According to his opinion, bile which enters the gallbladder under normal conditions never leaves the gallbladder. I am afraid that there are many facts which speak against this theory. The greatest difficulty for Dr. Halpert is that his theory is in opposition to these facts. What are the facts that show that the gallbladder normally delivers its contents every day? The facts are these: We have a dog with a permanent Pavlov's fistula of the common bile duct. If there is no food in the alimentary tract of such a dog, there rarely comes a flow of bile from this fistula. As soon as food is given to such a dog, it will be seen that first of all there is a discharge

through this fistula of thick bile containing mucin. The content of solid matter in such bile is in many cases in the first and second hour twice as great as in the later hours; in the later hours, from the third to the sixth hour, a straw-yellow bile is flowing. One may say that the liver is responsible for this dark viscid bile. Two investigators cut out the gallbladder, and in this case from the beginning of the experiment they received thin bile which did not contain mucin. Therefore there is no doubt that the thick mucin-containing bile flowing through the fistula shortly after a meal is from the gallbladder. That is the first fact which is hard to accept from the point of view of Dr. Halpert's theory.

The second fact is about the bile passages. We must not look on the bile passages as in passive use. They are in active use. They may let the bile run into the intestine or into the gallbladder. There are two sphincters which may regulate the flow of the bile, one in the common bile duct and another probably in the wall of the cystic duct or in the neck of the gallbladder. This is not a supposition to account for our facts. The dog has a double permanent fistula, a Pavlov's fistula of the ductus choledochus and a fistula of the gallbladder. Before the experiment the bile flows from the fistula of the gallbladder. As soon as food is given, conditions change, but it makes a great difference what food is given. If milk or meat is used no bile flows from the gallbladder during the first three to four hours. All the bile is directed to the common bile duct fistula. Later on, in the fourth or fifth hour, it flows in both directions; toward the common bile duct fistula and toward the gallbladder. When bread is given, conditions are different. In the first hour only the hepatic bile is directed toward the common bile duct. Later on the bile is flowing in both directions.

The third fact is that the gallbladder has the property to expel its contents into the duodenum. I will not discuss the property of the gallbladder to contract, because it is a complicated problem, and has no direct relation to our discussion.

The evidences of the fact that the gallbladder delivers its contents into the duodenum are so numerous that we could spend a whole night talking about them. Many investigators have shown that. I myself have reported some experiments on cats showing that the gallbladder is empty and collapsed after a meal containing cream and egg yolk. Dr. Halpert said that the gallbladder is emptied occasionally in small quantities. In my cases one hour after a fat meal only one or two drops of bile were left in the cat's gallbladder. I have been so interested that I asked our x-ray man at McGill University, Dr. Brooks, how things were going there. He told me that after the injection of dye in the morning, the gallbladder shows a good shadow, and after a standard meal consisting of cream and egg yolk in two hours the gallbladder is emptied and the shadow disappears, and he added that one can sometimes see this in the colon the next day. It is difficult to explain these facts from the theory of reabsorption of bile. Then we must make a highly improbable supposition that certain stimuli increase the absorption so much that in this short period of one or two hours the bile from the gallbladder is reabsorbed. If one adds to this certain data concerning the influence of nerves and drugs on the gallbladder, it will be seen that it is difficult not to believe that the contents of the gallbladder may be expelled into the duodenum. I would say that anybody who would like to say that this is not so will have a difficult task to prove that it is wrong.

I considered my invitation to address the members of these societies seriously, and therefore thought I would spend the time between when it was received, which was only about a week and a half, and this evening in trying to repeat experimentally Dr. Halpert's work. One fact in Dr. Halpert's work especially impressed me. His experiment with methylene blue is remembered. The methylene blue disappeared from the hepatic duct practically after thirty hours, but he could find the methylene blue in the gallbladder in something like seventy-two hours. Now, through what way had methylene blue reabsorbed from the gallbladder left the body? Did it get into the hepatic bile or into the urine to disappear completely? Maybe this bile had a third way to pass, and the third way was into the intestine. I performed the following experiments, only a few of which I shall quote. They answer this question of the bile passing into the intestine with a positive yes. The

first experiment was on a cat. With the animal under anesthesia, 6 cc. of 1 per cent methylene blue was injected into the gallbladder. The cat was left for six hours. After six hours the cat received 100 Gm. of cream and one egg yolk; then after two hours and twenty minutes, the cat was opened. The gallbladder was collapsed and almost empty. Two-tenths cubic centimeter of bile could be obtained from the gallbladder. The content of the first part of the duodenum consisted of yellowish-white masses. Further on there were greenish masses; so it could be interpreted that these experiments showed that bile from the gallbladder had already passed along and that later on hepatic bile poor in methylene blue was discharged.

The second cat received an injection of methylene blue. After five hours and twenty-five minutes, it received the same amount of cream and one egg yolk as the first cat. This cat did not eat the meal properly; she left part of it. The cat was opened about an hour and fifteen minutes after the test meal. The duodenum was filled with greenish-white masses. The common bile duct was cannulated. It could be seen that the bile which was flowing was dark green. This bile could be from the gallbladder or from the liver. The cystic duct was tied. Then this dark green bile was replaced by light brown bile. A remarkable phenomenon was observed: as soon as the light brown bile was placed in a cylinder and shaken with air, it turned green, and when the concentration of dye in both biles was compared it was found that it was about 2.4 times greater in the first bile than in the second. In other words, the first bile came from the gallbladder and the second bile from the liver.

The third experiment was done on a dog. Under anesthesia 5 cc. of bile was removed aseptically from the gallbladder (the gallbladder contained about 6 or 7 cc. of bile) and 5 cc. of 1 per cent methylene blue was injected. The next morning the dog was given a test meal of 250 cc. of cream and two egg yolks. After two hours and fifteen minutes the dog was opened under anesthesia. The gallbladder contained only 2 cc. of bile. The contents of the intestine was milkish yellow. This experiment could be interpreted in the sense of Dr. Halpert that the green bile with methylene blue was absorbed in the gallbladder and yet the fresh bile from the liver was flowing in the intestine. Hydrogen peroxide was added to the intestinal contents and the content turned green, but it was not yet proved that it was methylene blue because the bile under the influence of peroxide turned green (bilirubin could be converted into biliverdin). Therefore according to the method of Halpert lead acetate was added to this greenish content of the intestine, and after a certain time a light blue appeared which indicated that the dye injected into the gallbladder appeared in the intestine. I want to say only a few words about the reduction of the methylene blue. Apparently we have made an interesting observation that the bile removed from the gallbladder and mixed with methylene blue retains its green color for many days. I have had one such bile for seven days. The hepatic bile has the property to reduce methylene blue to a leuko-form. In the freshly secreted bile from the hepatic duct it seems there are substances which are able to reduce the methylene blue, and in the gallbladder bile there are certain substances which resist this reduction.

The last word is about the experiments on rabbits. One rabbit was given intravenous injections of methylene blue and left for five hours without food and then killed. The gallbladder was found to be practically empty; it contained less than 0.1 cc. of bile. Another rabbit was given injections with methylene blue also, but received food afterward. It was killed six hours later. The gallbladder contained 0.3 cc. of green bile only. The intestinal contents were yellow, but at that time the idea of reduction had not occurred. I must say the rabbit is a peculiar animal because its stomach is like that of no other animal. Its stomach is always filled with food, and it is constantly secreting pancreatic juice. Special experiments must be done to clear up the problem of discharge of the bile from the gallbladder into the duodenum in rabbits. My experiments show only that in both rabbits the gallbladders were practically empty. It is doubtful, however, whether the rabbit's gallbladder would react differently from that of other animals.

BÉLA HALPERT: I spoke of experiments with methylene blue in the rabbit and mentioned also the monkey. I may add to this that the experiment was performed once in man also, with a result much like that in the rabbit. Methylene blue was given by mouth in an amount used in the rabbit experiments, i. e., 20 mg. per kilogram of body weight to a woman, aged 37, on whom an operation was to be performed. One half of the dose was given eighty-six and the other seventy-four hours before laparotomy. The patient was kept on the usual hospital diet. The urine became free from methylene blue thirty-six hours before the operation. The bile removed from the gallbladder at operation, seventy-four hours after the last dose of methylene blue, contained the dye in a concentration (1:4,800) higher than in any of the similar experiments in rabbits.

STUDIES ON "MALIGNANT SCLEROSIS" OF THE KIDNEYS (FAHR). PAUL KLEMPERER and S. OTANI.

The studies were based on eighteen cases observed at Mount Sinai Hospital, New York City, and ample control material. In the cases studied, ten patients were males and eight were females. Seventy-two per cent of the patients were less than 50 years of age, while 28 per cent were older; this was exactly the reverse of the age incidence in sixty-two cases of benign sclerosis. The frequency of malignant sclerosis was evidenced by the fact that 34 per cent of all fatal cases of renal disease observed during the last two years were of this kind.

The essential clinical feature was hypertension of long duration with suddenly developing renal insufficiency which quickly led to the death of the patient. In two cases high blood pressure was incidentally discovered at the examination for life insurance. In the other instances, more or less severe symptoms, mostly headaches, failing vision, nosebleed or cardiac manifestations had caused the patients to consult a physician who had detected hypertension. Occasionally, the long duration could be concluded only from the marked hypertrophy of the heart, found at necropsy. The sudden occurrence of such serious symptoms as persistent vomiting, coma or stupor was the usual cause of the hospitalization of the patients. The duration of the terminal phase was from five days to five months; the average duration of all cases was thirty-nine days. The course of the disease in the terminal phase was always progressive, never was there a remission, and the patients died invariably despite every treatment. The clinical symptoms in fourteen cases were those of uremia—persistent vomiting, muscular twitchings, severe pruritus, restlessness and finally coma. The retention of nitrogen was extreme, values over 100 mg. urea nitrogen per hundred cubic centimeters of blood being the rule. In two of the remaining four cases without clinical symptoms of uremia, the figures of the urea nitrogen of the blood were over 100 mg. per hundred cubic centimeters of blood, proving the severity of the renal insufficiency. In the two other cases retention of nitrogen was present but was only moderate. Albumin, white cells and casts were always found, red blood cells were present in only a few cases. The specific gravity of the urine was always low with the exception of one case. When a concentration test had been done, it showed a low fixed specific gravity. Both the systolic and the diastolic blood pressure was always high, averaging 212/132 mm. Neuroretinitis was found in all cases with the exception of one in which the patient was not examined.

Macroscopically the surface of the kidneys was characterized by grayish-yellow granulations over depressed red areas. Though the granulations were always present, there were variations in the degree of atrophy. Only a few of the cases showed marked diminution in size, the average weight of all being 112 Gm. In every case petechial hemorrhages were seen on the surface and also on section; in three instances they were so numerous that the surface appeared riddled with smaller and larger hemorrhagic spots. The cross-section showed variations in the width of the cortex corresponding to the degree of atrophy, but the cortical markings were nearly always somewhat indistinct. There were always hemorrhages in the pelvic mucosa. Arteriosclerosis of the renal artery was conspicuous in only eight cases; but the arciform arteries appeared to be arteriosclerotic in the majority.

Coarse arteriosclerotic scars on the convexity of the kidneys, causing irregularities, were superimposed on the diffuse fine granulations in the majority of cases.

The histologic examination with low magnification showed various degrees of glomerular fibrosis and connective tissue replacement of the renal parenchyma. But even in the cases with marked fibrosis it was surprising to find that the majority of the glomeruli did not present prominent morphologic changes. In order to obtain a numerical measure, the glomeruli in fields of equal size were counted and classified according to the degree of morphologic alteration. Thirty-eight per cent showed such definite changes as complete or partial fibrosis, necrosis of the capillary tufts, epithelial or endothelial proliferation. The remaining 62 per cent appeared unaltered apart from collapsed capillaries as an evidence of a disturbance of their blood supply. The fibrosed malpighian corpuscles differed in no way from those found in arteriosclerosis of the kidney. There could be observed the various stages and modes of development of fibrosis, as collapse and fusion of loops, hyalinization and capsular thickening with gradual choking of the glomerulus. In nearly half of the damaged glomeruli severe degenerative and seemingly inflammatory changes were observed. The former were hyaline droplet degeneration of the internal and external capsular epithelium and necrosis of the capillary loops. The latter consisted of endothelial and epithelial proliferation with even occasional formation of crescents as in the extracapillary forms of subacute glomerular nephritis, accumulation of polymorphonuclear leukocytes within the capillary lumen and Bowman space, here often mingled with desquamated epithelium and occasional red blood cells. The glomerular alterations were not missed in any of the cases though there were variations in their frequency in the individual observation. However, it appeared logical to conclude from the percentage of their occurrence that the actual glomerular damage could not be held responsible for the severity of the renal insufficiency.

Furthermore, it was questioned whether the nuclear increase and epithelial proliferation within the malpighian corpuscles should be considered as actually inflammatory as Fahr believes, or merely as a reaction to ischemia. The presence of similar changes in severe renal arteriosclerosis (the benign decompensated sclerosis of Fahr) seemed to favor the latter view. The observation of identical glomerular changes in the periphery of recent bland renal infarcts was considered as further support for the view that they represented a reaction to ischemia. The glomeruli in such locations showed also clearly hyaline droplet degeneration which Fahr maintains to be toxic in origin. There could not be any doubt of the ischemic etiology in such instances as renal infarcts. The occurrence of these questionable glomerular changes, therefore, could not be considered as proof of the inflammatory nature and toxic origin of the malignant sclerosis.

The most outstanding changes, however, were not those of the glomeruli but necrosis of the arterioles and cellular proliferation of the distal portions of the interlobular arteries. These observations were in full accord with Fahr's description. The interpretation of these results, however, differed again from that of Fahr. He considers the arteriolar changes as inflammatory in nature, and toxic in origin and terms them necrotizing arteritis and arteriolitis. The reason for his conception is the occurrence of arteriolar-necrosis in subacute glomerular nephritis which changes he identifies with the arteriolar lesions in malignant sclerosis. However, our observation in several cases of subacute glomerular nephritis with severe arteriolar changes did not confirm Fahr's contention of their identity with the arteriolar-necrosis in malignant sclerosis. The arterioles in subacute glomerular nephritis showed not only necrosis but always intravascular and perivascular accumulation of polymorphonuclear leukocytes which were completely absent in the necrotic arterioles of our group. It was, therefore, correct to speak of necrotizing arteriolitis in subacute glomerular-nephritis but the term was not justified in the cases of malignant sclerosis observed by us.

Since glomerular changes as described by Fahr were found in simple ischemic conditions, it was logical to search here also for arteriolar-necrosis which was actually found in the vasa afferentia in the periphery of a recent bland infarct. This proved that arteriolar-necrosis can be an ischemic phenomenon.

The cellular intimal proliferation in small arteries has been considered by Fahr as productive endarteritis. If we followed the entire course of such interlobular arteries in serial section, we could observe that the proximal portions of the artery showed lamellations of the internal elastic membrane in the outer, and a cellular layer in the inner zone of the proliferated intima which was characteristic of arteriosclerosis. The distal portions, however, showed no elastica lamellations. It seemed, however, difficult to believe that the same vessel should be involved in two different pathologic processes, namely, arteriosclerosis in the proximal and endarteritis in the distal portions. It seemed rational to conclude that the cellular intimal proliferation was also arteriosclerotic in nature, the more so because no definite inflammatory reaction, such as intravascular or perivascular infiltration, could be observed in our cases. The proliferated cells suffered severe hyaline degeneration and fatty infiltration. The presence of foam cells next to the lumen caused marked narrowing, occasionally complete closure. The histologic picture suggested a rapid intimal proliferation with acute secondary degenerative changes. This acute narrowing could well have been responsible for ischemic changes in the arterioles and glomeruli and explained satisfactorily the ensuing circulatory disturbance of the remaining glomeruli. The arteriolar-necrosis and the glomerular changes are conspicuous features which permit the diagnosis of malignant sclerosis, but they are not of primary pathogenetic significance. They are not conclusive of an inflammatory origin of the renal disease. In fact, they are only secondary to a rapidly developing arteriosclerosis (Löhlein) of the interlobular arteries.

The term malignant sclerosis should be supplanted by such a clinical or anatomic descriptive name as "chronic hypertension with acute uremia or arteriolosclerosis—and necrosis of the kidneys."

#### DISCUSSION

ARTHUR M. FISHBERG: I cannot refrain from expressing to Dr. Klemperer and Dr. Otani the great pleasure I have had in listening to their splendid presentation. As far as terminology is concerned, I think the terms benign and malignant sclerosis are scarcely apt. These cases of so-called malignant sclerosis start as essential hypertension. In every one of the cases we have seen, the patient has shown evidence of having had hypertension of many years' duration. There was always marked cardiac hypertrophy. In other words, the process of arteriolar necrosis, which characterizes anatomically the so-called malignant sclerosis, is merely a complication of essential hypertension, and it is by no means the most frequent complication. The most common complication is cardiac failure. The second most frequent complication is cerebral hemorrhage, and the third is renal insufficiency which may or may not be due to arteriolar necrosis. For these reasons, I think a better term to use for the cases with arteriolar necrosis would be the malignant phase of essential hypertension. These patients have had essential hypertension for years, twenty in one of our cases, and the period characterized clinically by renal insufficiency and anatomically by arteriolar necrosis is merely one phase, the last.

Arteriolar necrosis is not the only cause of renal insufficiency in essential hypertension. There are at least three causes. One of these is the coalescence of the arteriosclerotic foci of atrophy in the kidney until so little intact parenchyma is left that the patient dies of uremia. Such patients are generally old. The second cause is cardiac failure, usually due to coronary disease, in patients whose concentrating power has already been moderately impaired. The third cause is the superimposition of arteriolar necrosis in the kidney.

It is perhaps worthy of emphasis, because of some recent statements in the literature, that the appearance of hypertensive retinitis in a patient with essential hypertension is not proof that there is arteriolar necrosis in the kidneys. I have seen cases of essential hypertension in which hypertensive retinitis developed, but at necropsy only "benign" changes were present in the renal arterioles.

Finally, I should like to add one more argument for the conception advanced by Dr. Klemperer and Dr. Otani that arteriolar necrosis is pathogenetically closely related to arteriolosclerosis, being presumably a more acute form of the latter.

It is known that arteriosclerosis has a characteristic distribution, being most marked in the kidneys; less so in the pancreas, spleen (here hyalinization of the arterioles is physiologic), liver and a few other organs; and totally absent in the voluntary muscles, though found extremely rarely in the myocardium. Arteriolar necrosis has this distribution, which would speak for a close relationship between the two processes.

HERMAN O. MOSENTHAL: We owe a debt of gratitude of more than the conventional sort to Dr. Klemperer for having worked up these cases which are among the first to demonstrate the presence of these lesions. I sincerely agree with Dr. Fishberg in regarding these pathologic changes as another example of the serious effects which hypertension has on the various organs. Dr. Klemperer has shown us that this necrotizing arteriosclerosis of the kidneys occurs in patients who had been the subject of hypertension for a long period, and what I believe is equally important and of great significance is that there was a rise in the diastolic as well as in the systolic pressure in these cases. This leads me to one other point, which is this: It seems to me that the term malignant in connection with hypertension is an extremely unfortunate one. In the first place, according to various students of this subject, it is applied to three distinct complications accompanying high blood pressure; thus its significance from either the pathologic or the clinical point of view is not clear. Furthermore, the terms malignant and benign are usually used in medicine in describing conditions entirely apart from a disease like essential hypertension. I believe it would be much more appropriate if the terms malignant and benign were dropped in this connection, and if we would simply classify these cases as mild or severe, and the criterion for such a classification would be the height of the diastolic pressure. Any patient with a diastolic pressure constantly at a level of about 130 mm. of mercury or above should be classed as a severe instance of essential hypertension, with the idea in mind that within a comparatively brief space of time there will develop in him lesions in the heart, brain or kidneys that will prove to be fatal. The diagnosis of the site of the pathologic change and its character, of course, cannot be made until the pathologic lesions actually develop. Dr. Klemperer has, I believe, furnished exact data as to another form of chronic interstitial nephritis in a complete and satisfactory way. The fact that we can trace these serious lesions in the kidneys to a definite cause, that is, a mechanical strain entailed by an increased blood pressure, is significant and adds a new feature to the etiology of acute diseases of the kidney.

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, May 13, 1929*

ESMOND R. LONG, *President, in the Chair*

### THE VALUE OF CULTURE IN THE DIAGNOSIS OF TUBERCULOSIS. H. C. SWEANY and MAX EVANOFF.

After several years of experimentation with culture mediums, we are able to recommend a method or combination of methods by which practically all viable tubercle bacilli can be grown. The percentage of positive results is slightly higher than that obtained by animal inoculation. Obviously, such procedures have greater value in diagnosis and save time and expense.

The growth becomes visible within two or three weeks, but acid-fast bacilli may be demonstrated within a week in stained preparations. The cost of a culture diagnosis does not exceed 20 cents, while a fair charge for diagnosis by animal inoculation is \$4.

There are a few rare lesions with cultural results not comparable to those with animal inoculation. In old fibrous lesions with attenuated bacilli and in some primary lesions of children, we have encountered difficulty in culturing tubercle

bacilli. Sometimes, we have failed to obtain growth when the material is overgrown with spore-forming bacilli. Success in such circumstances depends largely on the technic of treating the material with caustics.

Summarizing the results in the cultivation of human tubercle bacilli from lesions in man, we obtained the best growth with our "cream" medium and nearly as good with the "milk" medium. Both were better than Petroff's egg and Corper's potato mediums. With twenty-two lesions of various types and stages of healing, in which a diagnosis could not be made directly, growths were obtained by culture in 55 per cent and by animal inoculation in 35 per cent. There is little doubt that many of the lesions were entirely closed so that the true percentage for viable tubercle bacilli probably is much higher.

The germicides of choice are 3 per cent hydrochloric acid and 3 per cent sodium hydroxide, respectively, applied for from twenty to thirty minutes. While it is true that all acid-fast bacilli may not be tubercle bacilli, all of the numerous acid-fast micro-organisms that we have grown from material from man have the pathogenicity of tubercle bacilli. It is safe, therefore, to make a tentative diagnosis of tuberculosis by finding slow-growing, cribriform, waxy colonies of acid-fast bacilli.

From bovine tuberculous lesions we have commonly found acid-fast and semi-acid-fast micro-organisms that do not have the usual pathogenicity of this variety of tubercle bacilli. In fact, by our method of direct culture from the lesions it seems that there is a wide variation in strains of different lesions which diminish in virulence to saprophytes. Bacilli of high virulence seem to be obtained consistently only after passage through animals in which the associated weak forms appear to be overgrown by the virulent forms. For this reason, perhaps, our virulence tests do not correspond to those of Park. Some of these atypical strains appear to regenerate into the usual forms, while others are saprophytes. The early colonies of bovine tubercle bacilli on our cream medium sometimes appear soft and spreading, but assume the more crumblike form as they become older. Another striking feature concerning the bovine type is that no growth was obtained directly from seventeen lesions on medium containing fresh glycerin, but organisms in these grew on our cream medium without glycerin. This feature has been observed by Park and others with recently isolated bacilli, but not from true primary cultures. The bovine tubercle bacilli gradually gain avidity for glycerin when they are passed through guinea-pigs and are cultured.

The tubercle bacilli obtained from three lesions from hogs simulated, but were not identical with, those obtained from lesions from fowls. There seems to be a greater variation in the gross appearance of the avian forms than of the other types. The one diagnostic characteristic seems to be their ability to grow readily on practically all standard mediums for culturing tubercle bacilli. Confirmation by the usual pathogenicity tests is necessary.

#### LIPOSARCOMA OF THE MAMMARY GLAND. RICHARD A. LIFVENDAHL.

The rare occurrence of a liposarcoma of both mammary glands is here reported.

An Italian woman, aged 41, four months after the delivery of her fifth child, noted small soft masses in both breasts, which increased slightly in size for four months before her admission to the Cook County Hospital. The infant was nursing when the patient was admitted, and no general symptoms were present. Both mammae were removed without the pectoral muscles or the axillary lymph nodes.

Both glands were covered by coarsely wrinkled skin that had from ten to fifteen various sized nodular elevations of smooth contour. The nipples were not retracted and were without abnormal discharge. In the tissues were from ten to fifteen round and ovoid masses which involved three fourths of the right and one fourth of the left breast. They were located at various depths, none was adherent to the overlying skin and all were well circumscribed from the remaining yellow and grayish-white mammary tissue. They were composed of grayish-white and pale yellowish-white, moderately firm tissue, containing a glairy, colorless, mucoïd liquid. There were small hemorrhages in one of the nodes of the left breast. The



cytoplasm of the cells in the nodes contained lipid droplets. The cells varied markedly in size and shape; many were round or oval, and still others were spindle-shaped. The nuclei of those containing much lipid were at the periphery and were elliptical. Some of the cells contained two nuclei and some were in mitosis. The stroma consisted chiefly of a loose myxomatous tissue with widely separated various sized spindle cells containing various quantities of lipid.

The relatively normal tissue surrounding the tumor masses consisted of grayish-white streaks and bands with interspersed yellow material. These regions contained alveoli, some with large quantities of secretion. The ducts near the tumors were slightly flattened, and the intervening stroma was scanty.

The patient left the hospital; she died within three months after the mastectomy from what seemed clinically to be metastases of the lungs.

#### THE EARLY AND THE HISTOLOGICALLY HEALED END-STAGES OF PERIARTERITIS NODOSA. AARON ARKIN.

Periarteritis nodosa is a specific infectious disease probably caused by a filtrable virus, with an elective affinity for the arteries of the body. The organs most commonly involved are the kidneys, heart, liver, muscles, peripheral nerves and gastro-intestinal tract. Any organ or all may be affected.

The chief symptoms are a septic temperature, polyneuritis and polymyositis, hematuria or nephritis, abdominal cramplike pains and progressive emaciation. The great variability of the symptoms, pointing to involvement of various organs, and the tendency toward acute exacerbations are suggestive of periarteritis nodosa.

The pathologic changes hitherto described may be divided into three stages: (1) alternative-degenerative, (2) acute inflammatory and (3) granulation tissue. In practically all published accounts various stages of these changes are recorded in different organs. I have studied five cases of the disease.

In one acute case, the earliest change was a periarteriolar hemorrhage, probably due to an increased permeability of the endothelium. In other small arterioles, there were edema and fibrinous exudation without leukocytic infiltrations. The subintimal fibrinous or hyaline-like exudation often narrows or obliterates the lumen of the vessel. The fibrin may extend through the intima into the lumen of the vessel. In the larger arteries the changes often begin around the elastica externa. Later, leukocytes appear.

My report concerns the histologically healed end-stage, or scar tissue stages, of periarteritis. A patient, aged 26, suffered from a single severe illness with icterus, high fever, acute nephritis and hematuria. He died four years later of renal and cardiac insufficiency. The postmortem examination revealed a histologically healed periarteritis nodosa affecting all the organs of the body except the central nervous system. The contracted kidneys, hepar lobatum, myocardial scars, pancreatic and suprarenal gland atrophy and coronary stenosis were due to this disease.

Cardiac insufficiency which fails to react to digitalis, renal insufficiency with low specific gravity and reduced chlorides of the urine, progressive emaciation, abdominal pain and hepar lobatum have not been ascribed to this disease. Although the right and left coronary arteries were reduced to one-fourth their normal caliber, there were no symptoms of angina pectoris.

The characteristic histologic changes found were: (1) proliferation of the intima with the new formation of elastic fibrils, leading to stenosis or even complete occlusion of the arteries; (2) extensive destruction of the media, including the elastica interna or the entire wall of the vessel, with aneurysmal dilatation and thrombosis, and subsequent complete organization; (3) a periarterial healed granulation tissue mantle, consisting of dense fibrous connective tissue with capillaries and deposits of hemosiderin; (4) extensive destruction and even aneurysms in arteries with marked proliferation of the intima; (5) healed infarct scars of most organs, and (6) marked stenosis of both coronary arteries with destruction of their walls.

The hepar lobatum and extensive scars in different organs (due to infarction from arterial occlusion) demand a careful study of the arterial changes. Certain

livers, scarred like those in syphilis, may be so changed because of periarteritis nodosa. Elastic tissue stains should always be made.

# AN ANALYSIS OF THE NECROPSY STATISTICS OF A SECTARIAN HOSPITAL. O. T. SCHULTZ.

For the purpose of this presentation, sectarian hospitals are defined as those supported in whole or in large part by religious denominations. Christian has criticized hospitals supported by Jewish charity because of their supposed low percentage of necropsies, and similar criticism is directed also against those supported by Catholic organizations. The inference is that religious prejudice against necropsies is an important factor in the percentage figures for necropsies of such institutions.

At the Michael Reese Hospital, the percentage of permission for necropsy, which had been from 10 to 13 per cent up to 1921, increased suddenly in 1922 to 35 per cent and rose progressively to 56 per cent in 1927. The present hospital administration deserves a large share of credit for the sudden and continuous increase. The figures for 1926 and 1927 have been subjected to analysis in an attempt to determine, if possible, what factors, including the element of religion, may interfere with the gaining of permission for postmortem examinations. For such an analysis the necropsy service of the Michael Reese Hospital lends itself

TABLE 1.—Percentages of Necropsies by Services

	Ward			Private			Total		
	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage
Pediatrics .....	272	200	74 (79)	105	47	45 (53)	377	247	66 (78)
Medicine .....	96	39	41 (42)	135	37	27 (30)	231	76	33 (36)
Surgery .....	94	48	51 (55)	108	45	42 (51)	202	93	46 (53)
Gynecology and obstetric...	24	8	33 (31)	24	9	38 (50)	48	17	35 (38)
Total .....	486	295	61 (64)	372	138	37 (44)	858	433	50 (56)

well because: it is a general hospital of 557 beds; it is supported by the Associated Jewish Charities of Chicago; it combines both charity and private services (approximately 60 per cent of its work being charity); it is open to reputable physicians not members of its staff, and staff membership is not limited exclusively to physicians of Jewish faith. The religious belief of the patient is not a factor in his admission to the hospital. During 1926 and 1927, about 57 per cent of the patients were Jewish, the proportion being approximately the same for both charity and private patients. It is possible, therefore, to compare the necropsy percentages within the same hospital of both private and charity, and Jewish and non-Jewish patients.

The data which have been studied relate to 189 necropsies done in 1926, for which year the permission percentage was 45, and to 244 necropsies done in 1927, when the percentage was 56, a total of 433 necropsies in two years, which constituted 50 per cent of the deaths.

In table 1, the data are arranged according to services, the figures for 1927 alone being given in parentheses. The striking difference between the ward and the private services is apparent at once. Fifty-seven per cent of all deaths occurred in ward patients, but this number yielded 61 per cent of necropsies, whereas 43 per cent of deaths of private patients yielded only 37 per cent of necropsies. Also striking in this table is the high percentage for pediatrics, and the appreciably larger proportion of necropsies in surgical as compared with medical patients.

To determine if sex is a factor, the figures for adults, arranged according to sex, are given in table 2. Adult deaths made up 52 per cent of the total deaths in the hospital, and 54 per cent of the total adult deaths occurred in females.

There is no significant difference in the percentage of necropsies in deaths of adult male and female patients.

A comparison of the necropsy percentages in private patients of members of the hospital staff with those in private patients of physicians who are not members of the staff is given in table 3. At first glance the difference is not great enough to be significant in the mathematical sense, but it is actually greater than the mere percentage figures indicate, because 77 per cent of deaths of patients of staff members yielded only 36 per cent of necropsies, whereas 23 per cent of deaths of patients of nonstaff members yielded 39 per cent in necropsies.

The relation of religious faith to necropsy percentages, as given in table 4, is of greatest interest. A significant and striking difference is apparent in the necropsy percentages of both ward and private Jewish patients as compared with those of

TABLE 2.—Sex (Adults)

	Ward			Private			Total		
	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage
Female .....	104	43	41	137	49	36	241	92	38
Male .....	85	37	44	120	36	30	205	73	36
Total .....	189	80	42	257	85	33	446	165	36

TABLE 3.—Private Patients of Staff and Nonstaff Members

	Deaths	Necropsies	Percentage
Staff .....	288	105	36
Nonstaff .....	84	33	39
Total .....	372	138	37

TABLE 4.—Religion

	Ward			Private			Total		
	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage
Jewish .....	257	116	45	234	65	28	491	181	37
Non-Jewish .....	229	179	78	138	73	53	367	252	69
Total .....	486	295	61	372	138	37	858	433	50

non-Jewish patients. The difference is even greater than the table indicates, because the deaths of Jewish ward patients made up 53 per cent of all deaths of ward patients but furnished only 45 per cent of necropsies in this group. Sixty-three per cent of deaths of private patients occurred in those of Jewish faith, but permission for necropsy was obtained in only 28 per cent of such deaths. Necropsy was done in 181, or 37 per cent, of a total of 491 deaths of Jewish patients and in 252, or 69 per cent, of a total of 367 deaths of non-Jewish patients.

ENDOCARDITIS AS A SEQUENCE OF OSTEOMYELITIS. RUTH SISSON.

Metastatic infection of the valves of the heart from the diseased bone is occasionally referred to in accounts of osteomyelitis or of endocarditis as a possibility (Phemister, D. B.: *Nelson's Loose-Leaf Living Surgery*, 1928, vol. 3, p. 715. Aschoff, L.: *Pathologische Anatomie*, Jena, 1928, vol. 2, p. 29. Dyas, F. G.: *Surg. Gynec. Obst.* 7:555, 1908. Romberg, E.: *Lehrbuch der Krankheiten des*

Herzens und der Blutgefäße, 1925, p. 574. Osler, William; and McCrae, Thomas: Modern Medicine, vol. 4, p. 466). Some such references apparently are due more to an effort to have nothing left out of lists of what may occur than to any definite information about this rare sequence. Many standard works on surgery do not mention the infection (Lexer-Bevan: General Surgery, 1908. Lewis, D.: Practice of Surgery, 1927. Garré, G., and Borchard, A.: Lehrbuch der Chirurgie, 1923. DaCosta, J. C.: Modern Surgery, ed. 9, 1925. Duplay, S., and Reclus, P.: Traité de chirurgie, 1890-1892). I have been able to find only a few reports, and these are all of endocarditis following acute, rather than chronic, osteomyelitis. In one case reported by E. Fraenkel and A. Sängner (Untersuchungen über die Ätiologie der Endocarditis, Virchows Arch. f. path. Anat. **108**:286, 1887), the disease of the right tibia of a boy, aged 13 years, was attributed to *Staphylococcus aureus*, and only the front mitral leaflet became infected. The observations reported by T. Kocher and E. Tavel (Chirurgische Infektionskrankheiten, Basel and Leipzig, 1895, p. 124) occurred in boys, aged 15 and 17 years. In the younger, the osteomyelitis affected the right tibia and all leaflets of the tricuspid valve were involved; in the older boy, the left internal malleolus was affected, as well as all the tricuspid and mitral leaflets. In both patients the organism was staphylococcus. Much more recently, W. S. Thayer (Studies on Bacterial [Infective] Endocarditis, Johns Hopkins Hosp. Rep. **22**:35, 1926), in a bacterial study of endocarditis, referred to staphylococcal valve lesions due to osteomyelitis or epiphysitis in four patients. The valves impaired are not specified.

On account of the long duration of the illness, the many remissions and for other reasons to which allusion will be made presently, it seems likely that the aortic endocarditis in the following case was metastatic from an osteomyelitis.

*Clinical History.*—A man, aged 46, fell 25 feet, breaking both bones of both legs. The fractures of the right leg healed uneventfully, but seventeen days after the accident it was found necessary to fix the fragments of the left tibia with ivory pegs. (For these clinical details I am indebted to Dr. C. R. G. Forrester and Dr. Leroy Kuhn of Chicago.) There was some fever after the operation, the temperature being 101 F. on the third day, with a gradual drop to normal on the tenth day. A Wassermann test of the blood for syphilis gave negative results. The patient left the hospital in good condition, but one month later there was a small wound of the front of the left leg which still drained.

Six months after the first operation, considerable infected bone was found with the roentgen rays where the fragments of the left tibia had been pegged together, and after a second six months, there were three open draining fistulous passages. A sequestrum was removed at this time, and the infected tissues were curetted. There was a slight fever for five days. The patient left the hospital at the end of three weeks.

Four months later the wound was still draining and small fragments of bone were removed. Two months after this another sequestrum and one of the bone pegs were removed, and the curetted cavity was filled with adipose tissue from one buttock. His stay in the hospital this time was six weeks. Two months later the wound was still draining, and there was considerable inflammation of the leg. For this condition he was once more admitted to the hospital for six weeks, where hot boric acid fomentations and other local treatment were applied which again resulted in an apparent cure. During this period, he had a fever which lasted about a week, the highest rise in temperature being 102.6 F.

Another serious operation was found necessary three months later, at which time the front of the tibia was chiseled away, and part of a bone peg was removed with considerable bone that was honey-combed with fistulous passages. After this procedure the patient remained in the hospital for three months. Intermittent discharge from the wounds continued for the next eighteen months, and four years after the first operation he became acutely ill with what was regarded as pneumonia and died. From the record of the postmortem examination and subsequent studies, the following points are important:

*Necropsy* (Dr. E. R. LeCount).—The anatomic diagnosis was: ulcer of the left leg; chronic osteomyelitis of the left tibia; large defect of the tibia; healed fracture of the left tibia and fibula (malunions); bony union between the shafts of the left tibia and fibula; hyperplasia of the left inguinal lymph glands; thrombo-ulcerative aortic endocarditis; multiple infarcts of the kidneys and spleen; embolic hemorrhages in the brain; acute hemorrhagic nephritis; hypertrophy of the left ventricle of the heart; hypostatic hyperemia of both lungs, and chronic catarrhal bronchitis.

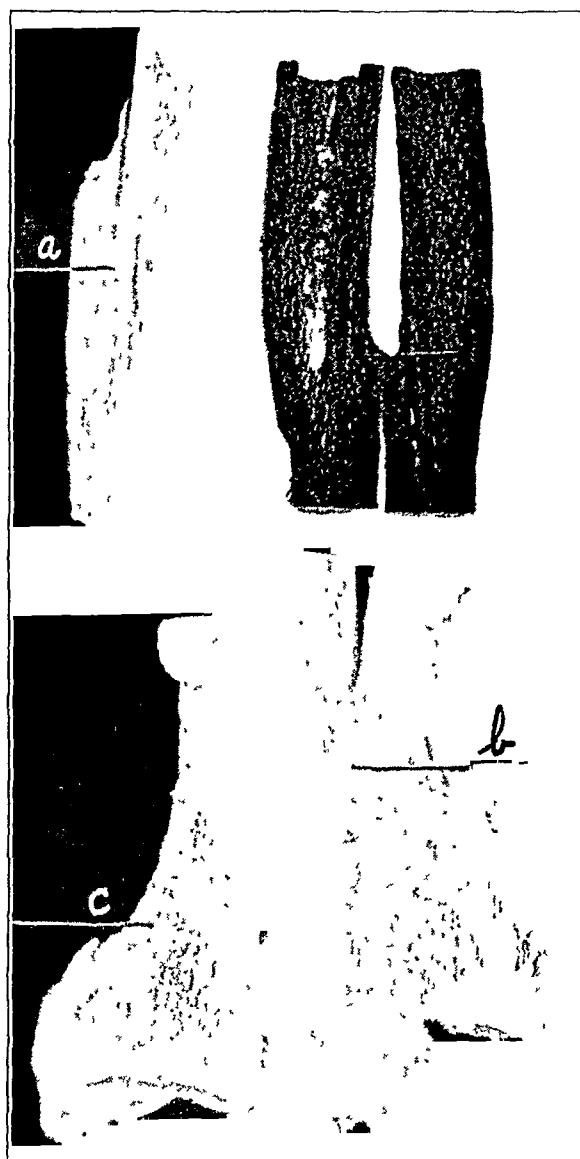


Fig. 1.—The lower end of the tibia and fibula, grown together, were sawed in a plane diagonally from in front back and out. The segment of the malunited fibula in the upper left hand corner has not been cut lengthwise. *a*, fibular malunion; *b*, bony union of the tibia and fibula; *c*, osteomyelitic cavity.

As a mass, the lymph glands of the left groin were twice the size of those of the right. No gross evidence of suppuration was found in them. There was an ulcer of the inside and ventral surfaces of the distal third of the left leg, which was 6.5 cm. long and from 10 to 15 mm. wide. Its distal end was 5 cm. above the

level of the malleoli, and its bottom was deep in a defect of the tibia. Sixteen centimeters above the distal end of the fibula, the lower end of the upper fragment made when the bone was broken lay on the outer surface of the upper end of the lower fragment. This overlapping was 3.5 cm. long, and the two fragments were firmly joined by compact bone. As a result the upper portion of the shaft of the fibula was completely out of vertical alinement with the distal part (fig. 1, *a*). Beginning 5.5 cm. above the distal end, the fibula was firmly united to the tibia for 4 cm. by compact new bone slightly more abundant externally and ventrally than behind (fig. 1, *b*).

The fracture in the tibia began about 1 or 2 cm. distal to that in the fibula and was healed without much deformation of the shaft. The defect in the tibia began 2 cm. from the articular surface for the talus, was 9.5 cm. long, shallow and indefinite at its proximal end and was deep distally (fig. 1, *c*). The bone lining this cavity was irregular, with shallow and deeper small pits, a fine mosslike network of superficial furrows and sharp brittle delicate spicules a few millimeters long in its deepest portion. The adjacent surfaces of two of the aortic leaflets



Fig. 2.—A microscopic preparation of the two most involved aortic valves, enlarged about 4 diameters. *a*, cocci along the ventricular edge; *b*, the common junction of the leaflets nearest the aorta.

were firmly grown together so that they had a common free edge for 7 mm. out from their joined commissure. Pink fibrin covered about one half of the ventricular surfaces of each of these cusps, and on the corresponding surface of the third cusp, that from the sinus where the front coronary has its mouth, there was a rough red place from 6 to 7 mm. in diameter. Infarcts, some with gray centers, occupied about two thirds of the surfaces made when the spleen was cut in different places. The spleen was 12 by 9.5 by 5.3 cm. One infarct in the right kidney was 20 by 11 mm. in two of its dimensions. One in the left was almost as large, and in this kidney there was also a smaller infarct; in both kidneys there were small hemorrhages.

*Histology.*—There were large masses of gram-positive cocci without any chain formation on the ventricular edge of the aortic leaflets (fig. 2, *a*) and smaller masses in other focal lesions of the brain, kidney and heart muscle. Those in the kidney were small, few and wide apart in the central parts of the infarcts and more abundant in the periphery, especially the edge toward the pelvis. There

were also minute foci (0.3 mm. in diameter) deep in the medullary pyramids where infarcts were absent. The focal lesions in the heart were widely scattered and very small; some occupied no more than the space taken by seven muscle fibers cut squarely across; other lesions of the heart consisted solely of scattered leukocytes in lesions less sharply demarcated. In the sections of the lymph glands of the groin on the affected side there was simply hyperplasia. In the suprarenal glands, liver, pancreas and other organs no noteworthy change was found.

There is no certainty that the infection of the heart owed its origin to the osteomyelitis. However, the frequent attacks of fever, the number of operations, the persistence of the infection of the leg, the absence of a history of any other illness from which the endocarditis might have had its origin, the failure to find any other disease in the body to which it might have been secondary and finally the staphylococcus nature of all of the lesions are strongly in favor of the mode of death suggested by the title and the anatomic diagnosis.

## Book Reviews

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PRINCIPLES OF PATHOLOGY FOR PRACTITIONERS AND STUDENTS. By D'ARCY POWER, M.D., F.R.P.S., Professor of Pathology, College of Physicians and Surgeons, San Francisco; and WILLIAM W. HALA, M.D., Assistant Professor of Pathology, Long Island College Hospital, Brooklyn. Price, \$10. Pp. 787, with 298 illustrations, many in color. New York: D. Appleton & Company, 1929.

For the most part the book is built on the conventional plan of textbooks of pathology. It is divided into two main parts: general pathology and systemic pathology. Contrary to the usual custom, general disturbances of the circulation are considered under the vascular system in the special part, which includes all the organs except the eye and the ear. There is an appendix with notes on microscopic technic, photography, theory of cell heredity, the Ehrlich nomenclature, protein nomenclature, the biochemical reactions of the body and sedimentation of the erythrocytes. The index seems to be complete and accurate.

A peculiarity of the book is the division of the text into consecutively numbered sections, 1,077 in all, a system which was adopted to facilitate cross references. This is a good principle because much space may be saved by reducing more than customary the repeating of descriptions of the same processes in the section devoted to general pathology and in the various subdivisions of systemic pathology. The main characteristics of tuberculosis, for instance, are the same no matter what its location, and there is no real need for repeated descriptions of these characteristics.

It is easy to find more or less minor faults with this book, but the essential teachings may be regarded as acceptable. The main fault with the book is that it does not reflect sufficiently the best kind of scholarship in modern pathology. It does not represent any advance over existing books in its field in either the style of writing, the matter of illustration, or the choice and treatment of subjects. Many of the illustrations are crude, some are indistinct, and taken as a whole they fall short of reasonable modern requirements. The book does not appear to meet any need that is not fully met by other books.

DIE MORPHOLOGIE DER MISSBILDUNGEN DES MENSCHEN UND DER TIERE. Ein Hand- und Lehrbuch für Morphologen, Physiologen, Praktische Aerzte und Studierende, Herausgegeben von DR. G. B. GRUBER, o.ö. Professor der pathologischen Anatomie an der Universität Innsbruck. Unter Mitwirkung zahlreicher Fachgenossen, begründet von WEIL and PROF. DR. ERNST SCHWALBE. III. Teil: Die Einzelmissbildungen. XIII. Lieferung. 3. Abteilung. 4. Kapitel: Die Missbildungen des Darmkanals und der Verdauungsdrüsen, Einschliesslich der Kloakenmissbildungen. Von PRIVATDOZENT DR. H. E. ANDERS. Paper. Price, 7.50 marks. Pp. 107, with 60 illustrations. Jena: Gustav Fischer, 1928.

Previous sections of Schwalbe's monumental work on "The Morphology of Monstrosities and Abnormalities of Man and Animals" have been reviewed in the ARCHIVES OF PATHOLOGY (4:504 [Sept.] 1927).

The present sections deal with abnormalities of the digestive tract, including the liver and pancreas. There is an introductory chapter on normal development, followed by a detailed consideration of the abnormalities of position, persistence of portions of the embryonal intestinal tract, defects of development, reduplications and gigantism, stenosis and atresias and finally congenital dilatation and diverticulation of the various parts of the gastro-intestinal tract. The final two chapters deal with the developmental disturbances of the pancreas and liver. There is a list of 372 references, most of which are to the German literature.



Many of the illustrations are schematic. The treatment of the various subjects is exhaustive and yet concise. Schwalbe-Grüber's work will for many years be the best reference book on the complicated but important subject of developmental faults.

**DISEASES OF THE THYROID GLAND.** By ARTHUR E. HERTZLER, M.D., Surgeon to the Halstead Hospital, with a chapter on Hospital Management of Goiter Patients by VICTOR E. CHESKY, M.D., Associate Surgeon to the Halstead Hospital. Ed. 2. Entirely rewritten. Price, \$7.50. Pp. 286. St. Louis: C. V. Mosby Company, 1929.

The title is a little too comprehensive, as the book deals mainly with goiter and surgical treatment for this condition. There are ten chapters: etiology of goiter; normal anatomy of the thyroid gland; pathologic anatomy of the thyroid gland, dealing mostly with goiter; symptoms of goiter; diagnosis; prognosis and treatment; goiters in unusual places; hospital management of patients with goiter (by Victor E. Chesky); topographic anatomy of the thyroid gland, and operative technic. Chapter three, on pathologic anatomy, occupies seventy-seven pages and includes a summarizing description of carcinoma and sarcoma of the thyroid gland.

Goiters are classified as colloid, as adenomas or nodular goiter without toxic symptoms, as adenomas with toxic symptoms, and as exophthalmic goiter, all of which are interpreted as stages of one progressive disease. The gross and microscopic descriptions are brief and clear with a tendency to oversimplification. Graves' disease is defined as toxic goiter due to the abnormal activity of newly formed acini developing from interstitial cells, while the term Basedow's disease is limited to those cases of toxic goiter in which disease of the eye is present. Fetal adenoma is treated as a true tumor; it is given great importance as the main source of carcinoma of the thyroid gland, and for that reason its removal is recommended on the same general principle as the removal of moles may be recommended, as a precautionary measure. The author, who is a surgeon, is fascinated with his study in which he is concerned mainly in establishing the true relationship of the clinical manifestations of goiter to the structural changes in the thyroid gland, but he does not discuss the fundamental problems of the physiology, normal and abnormal, of the thyroid gland. The presentation throughout the book is of a general and summarizing character, and there are no records given of the results of the systematic and thorough study of individual cases.

The consideration of the interstitial changes in goiter is limited mainly to the following statement: "There is yet to be considered a peculiar type of gland that must be considered apart from the general subject of the pathology of goiter. The only excuse for considering them here is that they too often lure the surgeon into performing a useless operation. These represent the type which some internists correctly associated with a peculiar type of person; slender of build, delicate skeleton, vivacious rather than intelligent, often bright eyed, in short, the type of girl depicted in automobile advertisements. Their goiters are never large, are elastic rather than firm, generally located high up on their long slender necks. The goiter cuts like rubber and is finely granular in appearance. Microscopically, the striking feature is the abundant lymphocytic infiltration and large number of lymph follicles. In a previous publication I expressed the opinion that they never contained germinal areas, but I have since seen specimens in which they were present. In addition, lymph glands the size of a bean are commonly found in the carotid group of lymphatics. This type may be called interstitial, for what little cellular changes they show is in the interstitial cells. The striking part of the picture is the flatness of the acinal epithelium. The increase of the colloid is never great, corresponding to the fact that in the clinic the thyroid gland is seldom larger than what one may describe as easily palpable, the impressive change being in the greater firmness of the gland. With such a picture one need not be surprised that little or no improvement is gained from operative removal of a part of the thyroid. Since this type is so generally associated with menstrual

disturbances, it seems that it should not be regarded as a thyroid disease at all, but merely a part of a general endocrine disturbance. In the severer cases there is an associated aplasia of the ovaries, and probably also a pituitary deficiency as well."

The author states his belief that the relationship set forth will gain recognition with time. The question of the influence of iodine on the structure of toxic goiter is not discussed, but in the preface reference is made to the work of Alexander Hellwig on this problem (*Surgery, Gynecology and Obstetrics with International Abstract of Surgery* 47:173, 1928), using material from the author's clinic. The illustrations in the book are creditable.

ETIOLOGIE ET PROPHYLAXIE DE LA GRIPPE. By R. DUJARRIC DE LA RIVIÈRE. Monographs of the Pasteur Institute. Price, 32 francs. Pp. 105, with 15 illustrations. Paris: Masson & Cie, 1929.

The author has presented this short readable monograph on the subject of influenza, apparently with an idea of bringing together current opinions and ideas on technic, more or less as a basis for future work. The book is divided into a short introduction covering the epidemiology, a major chapter on Pfeiffer's bacillus, a general chapter on the concept of the filtrable virus, and a discussion of the prophylaxis. A bibliography of 221 references is included, apparently fairly complete but poorly arranged. The fifteen excellent double photographic plates show the morphologic, microscopic and macroscopic aspects of Pfeiffer's bacillus and also several other hemoglobinophilic species.

The discussion of the epidemiologic phases is evidently intentionally cursory. In his discussion of Pfeiffer's bacillus, some emphasis is laid on the technic of isolation with which the author is familiar. The necessity for blood, the considerations of growth accessory factors, and the general cultural details are carefully described. Discussion of the pathogenicity of this organism covers most of the common laboratory animals and also experimental work on monkeys and on man. Serologic characteristics are briefly discussed, together with the means of identifying Pfeiffer's bacillus among the group of hemoglobinophilic bacteria with which it might be confused. In discussing the possible filtrable virus of influenza, the author apparently attempts to list impartially arguments for and against this etiologic agent. The chapter is carefully completed by discussing in some detail the *Bacillus pneumosintes* of Olitsky and Gates, and also by discussing the possibility of the filtrable forms of Pfeiffer's bacillus. He mentions that the proof of true filtrability is often lacking. His discussion of prophylaxis contains virtually nothing new.

If the reader of this monograph has not been converted to any one of the theories of influenza, he is left with the impression that Pfeiffer's bacillus perhaps merits more respect than it has been given in many quarters and that the author of this monograph perhaps has not given theories, other than that the etiologic agent of influenza is the Pfeiffer's bacillus, all the opportunities that they should have.

## Books Received

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METHODS AND PROBLEMS OF MEDICAL EDUCATION (Twelfth Series). Departments and Institutes of Roentgenology and Radiumtherapy. New York: The Rockefeller Foundation, 1929.

These bulletins are intended for distribution to teachers and administrators in medical schools and hospitals. Separate reprints and a limited number of volumes are distributed gratis to other interested persons on application to the Rockefeller Foundation, 61 Broadway, New York.

ABSTRACTS OF THESES, UNIVERSITY OF CHICAGO SCIENCE SERIES. Volume 6. Pp. 376. Chicago: University of Chicago Press, 1927-1928.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. Volume 12. Pathology of the Acute Respiratory Diseases and of Gas Gangrene Following War Wounds. Prepared under the direction of Major Gen. M. W. Ireland, Surgeon General. By Major George R. Callender, M.C., and Major James F. Coupal, M.C. Price, \$3.60. Pp. 583. Washington, D. C.: U. S. Government Printing Office, 1929.

SEVENTEENTH ANNUAL REPORT, MEDICAL DEPARTMENT, UNITED FRUIT COMPANY. Pp. 381. Boston: 1928.

A HISTORY OF THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. By P. M. Ashburn, Colonel, Medical Corps, U. S. Army, author of "The Elements of Military Hygiene." With an introduction by Surg. Gen. Merritte W. Ireland. Price, \$5.00. Pp. 448. Boston: Houghton Mifflin Company.

PRINCIPLES AND PRACTICE OF ELECTROCARDIOGRAPHY. By Carl J. Wiggers, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland. Price, \$7.50. With 61 illustrations. St. Louis: C. V. Mosby Company, 1929.

CLINICAL LABORATORY METHODS. By Russell Landram Haden, M.A., M.D., Professor of Experimental Medicine, University of Kansas, School of Medicine, Kansas City, Kan. Third edition. Price, \$5.00. Pp. 317, with 69 illustrations and 4 color plates. St. Louis: C. V. Mosby Company, 1929.

A MANUAL OF EXTERNAL PARASITES. By Henry Ellsworth Ewing, United States Bureau of Entomology. Price, \$4.50; by mail, \$4.66. With 96 illustrations. Springfield, Ill.: Charles C. Thomas.

COLLECTED STUDIES FROM THE BUREAU OF LABORATORIES, Department of Health, City of New York. Dr. William H. Park, director. Volume 10, 1920-1926. New York: Department of Health.

THE CLINICAL ASPECTS OF VENOUS PRESSURE. By J. A. R. Eyster, B.S., M.D., professor of physiology, University of Wisconsin, associate physician, Wisconsin General Hospital, Madison, Wis. Price, \$2.50. Pp. 135. New York: The Macmillan Company, 1929.

HUMAN HELMINTHOLOGY. By Ernest Carroll Faust, Ph.D., professor of parasitology in the College of Medicine of Tulane University, New Orleans. Cloth. Price, \$8.00, net. Pp. 616, with 297 illustrations. Philadelphia: Lea & Febiger.

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT. Im Auftrage des Vorstandes herausgegeben von dem derzeitigen Schriftführer, G. Schmorl, in Dresden. Vierundzwanzigste Tagung gehalten in Wien, 4-6, April, 1929. Pp. 388, with 149 illustrations. Jena, Austria: Gustav Fischer, 1929.

## AN INTERPRETATION OF MALIGNANT GROWTH BASED ON THE CHEMISTRY OF CELL DIVISION\*

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PHILADELPHIA

Proliferation of cells is the common defining characteristic of all malignant growths. It follows that the problem of malignancy centers itself primarily on the processes of cell reproduction. The question of inciting agents is secondary, since all these produce but one biologic reaction, namely, cell proliferation. Once the chain of reactions leading to increase in cell number has been set off in a receptive field, further development depends on the intrinsic biologic characteristics of the tissue in which the growth is taking place, regardless of the nature of the agent which upsets the previously existing equilibrium.

Now cell division is the expression of underlying physicochemical processes. The physical forces condition the degree of the reaction, the nature of which is determined by the type of the interreacting chemical groups and molecules. It is therefore clear that the most logical way to approach the problem is through a study of the chemical processes specific for growth by increase in cell number.

The nub of the matter rests on the knowledge of the chemical stimulus or stimuli specifically essential to cell division. This is primary. All else is secondary. The difference in H-ion concentration of the malignant cell as compared with the normal,<sup>1</sup> the difference in carbohydrate metabolism,<sup>2</sup> the difference in proteolytic activity,<sup>3</sup> all these, and more, are but sequelae of the heightened reproductivity of the cell.

\* Submitted for publication, June 10, 1929.

\* From the Research Institute of the Lankenau Hospital.

1. Millet, H.: Measurements of the  $p_H$  of Normal, Fetal, and Neoplastic Tissues by Means of the Glass Electrode, *J. Biol. Chem.* **78**:281, 1928. Harde, E., and Henri, P.: Sur le  $p_H$  des néoplasmes et des embryons de souris déterminé par la coloration vitale, *Compt. rend. Soc. de biol.* **96**:335, 1927.

2. Warburg, O.: Milchsäuregärung der Tumoren, *Klin. Wchnschr.* **6**:2047, 1927. Baker, S. L.; Dickens, F., and Gallimore, E. J.: The Glycolytic Action of Some Tumors and the Effect of Insulin, *Brit. J. Exper. Path.* **10**:19, 1929. Crabtree, H. G.: The Carbohydrate Metabolism of Certain Pathological Overgrowths, *Biochem. J.* **22**:1289, 1928. Cori, C. F., and Cori, G. T.: The Carbohydrate Metabolism of Tumors: II. Changes in the Sugar, Lactic Acid, and  $CO_2$ -Combining Power of Blood Passing Through a Tumor, *J. Biol. Chem.* **65**:397, 1925.

3. Carrel, A., and Ebeling, A. H.: The Fundamental Properties of the Fibroblast and the Macrophage: III. The Malignant Fibroblast of Sarcoma 10 of the Crocker Foundation, *J. Exper. Med.* **48**:105, 1928.

It is not enough to postulate the existence of a "Wund- or Teilungshormon," as Haberlandt <sup>4</sup> has done, or to assume the directive influence of an "archusia" and "ergusia," as Burrows <sup>5</sup> has done. These are mere words, and words have yet to solve a scientific problem. What is necessary is information as to the chemical groups concerned. Studies in this direction were undertaken at this institute about two years ago.

#### EVOLUTION OF THE SULPHYDRYL HYPOTHESIS

It occurred to me that the metal lead might serve as a reagent for identifying the growth-promoting stimulus, since Bell <sup>6</sup> had reported that growth is retarded thereby, and since lead is commonly used as a precipitant of biologic agents.<sup>7</sup>

It was first necessary to determine if the inhibitive influence of lead is exerted on growth by increase in cell number or on growth by increase in cell size.

It was found that the metal specifically retards cell proliferation and not cell assimilation.<sup>8</sup> Further, it was found that a well defined deposit of a lead-containing compound occurred in the regions of active cell division,<sup>9</sup> and that this concentration was associated with the nuclear activity of mitosis.<sup>10</sup> These data led to the conclusion that the metal, by precipitation, removes from activity some compound essential to cell reproduction.

Chemical studies under the microscope and of extracts in vitro brought out the fact that the lead-containing compound deposited in the region of active cell proliferation is a combination between the metal and sulphydryl. This, taken with the fact that sulphydryl is also found

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4. Haberlandt, G.: Ueber Zellteilungshormone und ihre Beziehung zur Wundteilung, Befruchtung, Parthenogenesis und Adventivembryonie, *Biol. Zentralbl.* **42**:145, 1922.

5. Burrows, M. T.: Studies on the Nature of the Growth Stimulus in Cancer, *J. Cancer Research* **10**:239, 1926.

6. Bell, W. B., and Patterson, J.: The Effect of Metallic Ions on the Growth of Hyacinths, *Ann. Applied Biol.* **13**:157, 1926.

7. Hopkins, F. G.: An Autoxidizable Constituent of the Cell, *Biochem. J.* **15**:286, 1921.

8. Hammett, F. S.: Studies in the Biology of Metals: IV. The Influence of Lead on Mitosis and Cell Size in the Growing Root, *Protoplasma* **5**:535, 1929. Hammett, F. S., and Wallace, V. L.: Studies in the Biology of Metals: VII. The Influence of Lead on the Development of the Chick Embryo, *J. Exper. Med.* **48**:659, 1928.

9. Hammett, F. S.: Studies in the Biology of Metals: I. The Localization of Lead by Growing Roots, *Protoplasma* **4**:183, 1928.

10. Hammett, F. S.: Studies in the Biology of Metals: III. The Localization of Lead Within the Cell of the Growing Root, *Protoplasma* **5**:135, 1928. Hammett, F. S., and Justice, E. S.: Studies in the Biology of Metals: V. The Selective Fixation of Lead by Root Nuclei in Mitosis, *ibid.* **5**:542, 1929.

concentrated in the regions where growth by increase in cell number is enhanced, led to the hypothesis that the nuclear activity of cell division is importantly factored by sulphhydryl ( $-\text{SH}$ ).<sup>11</sup>

The next step was to test the hypothesis.

#### EXPERIMENTAL DATA IN SUPPORT OF THE SULPHYDRYL HYPOTHESIS

By a variety of rigidly controlled tests made with extracts, and with synthetic and naturally occurring sulphhydryl compounds, on both plant and animal material, it was definitely established that the sulphhydryl group is stimulative to cell division specifically, growth by assimilation not being accelerated. This result, taken together with the work as a whole, has led to the conclusion that sulphhydryl is the essential stimulus to growth by increase in cell number.<sup>12</sup> A large mass of correlated data, reviewed in the paper cited, is thoroughly consistent with this conclusion.

Having thus identified a definite chemical group as specifically important in cell proliferation, the next step was to see whether or not the chemical data from the field of malignancy agree therewith, to see whether or not the etiologic concepts are explicable thereby, and tentatively to postulate an interpretation that might be used as a starting point for further exploration.

The chemical studies of sulphur metabolism in malignancy are meager and scientifically not all that is desired. Adequately controlled investigations of the sulphur partition in blood and urine are needed. What data there are have been collected in the admirable monograph of Kahn and Goodridge.<sup>13</sup> They indicate that the neutral sulphur fraction of the total sulphur is enhanced. Since this is composed of volatile sulphides, cysteine, cystine and similar suboxidized forms, the crude observations thus far made are consistent with the hypothesis that malignancy basically is the result of a distortion of sulphhydryl equilibrium.

These gross observations may by no means be taken as specifically diagnostic. Other diseases show a like distortion of the sulphur excretion. This does not mean that the observations have no significance and should be discarded. On the contrary, their very inadequacy should stimulate investigations not only of the nature of the components of the neutral sulphur fraction, but also of the relative quantities in different diseases. This field needs cultivation.

11. Hammett, F. S.: *Studies in the Biology of Metals: VI. The Nature of the Lead Compound Deposited in the Growing Root*, *Protoplasma* **5**:546, 1929.

12. Hammett, F. S.: *The Chemical Stimulus Essential for Growth by Increase in Cell Number*, *Protoplasma*, 1929, vol. 7.

13. Kahn, M., and Goodridge, F. G.: *Sulfur Metabolism: A Review of the Literature*, Philadelphia, Lea & Febiger, 1926.

Consistent with the finding of a relative increase in the excretion of neutral sulphur is the report of Roffo<sup>14</sup> that in animals with tumor the reducing power of the blood serum increases along with the tumor. This is probably not due to increase of sugar,<sup>15</sup> but to increase of sulphhydryl-containing compounds.<sup>16</sup>

When it comes to the chemical analysis of tumor tissue, the data are more satisfactory. Although the values for total sulphur are inadequate for the drawing of any conclusion, since proper controls were not had, they do show a trend toward increased amount.<sup>13</sup>

They thus are consistent with the idea of an association between malignancy and sulphhydryl.

The really significant observations are those of Voegtlin and Thompson.<sup>17</sup> These careful and competent investigators demonstrated that the living part of tumor tissue contains high concentrations of sulphhydryl. In fact, the amounts were comparable to those present in the liver, one of the organs richest in this chemical group. Although Yaoi and Nakahara<sup>18</sup> did not obtain like results, the results of Voegtlin and Thompson have been definitely confirmed by Lecloux, Vivario and Firket,<sup>19</sup> and the relation can be considered as established.

Indirect evidence that sulphhydryl is concentrated in tumor tissue is also available. Roffo and Correa<sup>20</sup> succeeded in isolating an insulinoid substance from malignant growths. The significance of this lies in the fact that insulin has been shown to contain suboxidized sulphur<sup>21</sup> and to be stimulative of cell proliferation in old ulcers of the leg,<sup>22</sup> though I found it unreactive for roots and paramécia.<sup>12</sup>

Further, Russell and Gye<sup>23</sup> observed that the oxygen consumption of cancerous tissue in the mouse rises with increasing speed of growth,

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14. Roffo, A. H.: Poder reductor del suero de ratas con tumores malignos, *Bol. Inst. de med. exper. para el estud. y trat. del cáncer* **4**:24, 1925.

15. Theis, R. C., and Stone, W. S.: A Study of the Chemical Composition of the Blood in Cancer, *J. Cancer Research* **4**:349, 1919.

16. Hunter, G., and Eagles, B. A.: Non-Protein Sulfur Compounds of Blood: II. Glutathione, *J. Biol. Chem.* **72**:133, 1926.

17. Voegtlin, C., and Thompson, J. W.: Glutathione Content of Tumor Animals, *J. Biol. Chem.* **70**:801, 1926.

18. Yaoi, H., and Nakahara, W.: The Glutathione Content of Chicken Sarcoma, *Biochem. J.* **21**:1277, 1927.

19. Lecloux, J.; Vivario, R., and Firket, J.: Teneur en glutathion du sarcome et des tissus normaux, *Compt. rend. Soc. de biol.* **97**:1823, 1927.

20. Roffo, A. H., and Correa, L. M.: La existencia de insulinoïdes en los tumores malignos, *Bol. Inst. de med. exper. para el estud. y trat. del cáncer*, 1926, no. 14.

21. Du Vigneaud, V.: The Sulfur of Insulin, *J. Biol. Chem.* **75**:393, 1927.

22. Aldersberg, D., and Perutz, A.: Beeinflussung der Regenerationsfähigkeit der Haut durch lokale Applikation von Insulin, *Klin. Wchnschr.* **6**:108, 1927.

23. Russell, B. R. G., and Gye, W. E.: The Oxygen Consumption of Normal and Cancerous Mouse Tissues in Vitro, *Brit. J. Exper. Path.* **1**:175, 1920-1921.

and Warburg, Wind and Negelein<sup>24</sup> found that a diminution of oxygen supply below a certain level kills tumor cells within the body. This heightened demand for oxygen is what would be expected from the fact of increased concentration of sulphydryl. For, as shown by Hopkins and Dixon,<sup>25</sup> the sulphydryl group is a reducing group, avidly taking up oxygen and going over to the —S.S.— form.

Finally, Mueller<sup>26</sup> reported that the rapid auto-inactivation of the filtrate of the Rous fowl sarcoma is due to oxidation. Such oxidation may be prevented by cysteine. Oxidation produces in compounds containing sulphydryl a like loss of the activity stimulative of cell proliferation.<sup>12</sup> Also, Harde<sup>27</sup> reported that the virulent activity of Rous sarcoma is lost in alkaline solutions, but intensified by appropriate acidification. And it is a fact that the sulphydryl group is rapidly oxidized in alkaline mediums, but remains fairly stable in acid.<sup>28</sup> Thus, the sulphydryl group and the sarcoma virus behave alike as regards activity after autooxidation and exhibition to alkali. The concordance is noteworthy. Although it may be that the active agent of the Rous virus is itself not sulphydryl, the foregoing data indicate that its effectiveness is related thereto.

These several data make necessary a serious consideration of the hypothesis that a heightened sulphydryl reactivity of the tumor-producing cells is an important factor in, if not the fundamental cause of, tumors.

#### INTERPRETATION OF PRESENT ETIOLOGIC CONCEPTS OF MALIGNANCY IN TERMS OF THE SULPHYDRYL HYPOTHESIS

There are two possibilities. The cells that proliferate to malignancy are either inherently abnormally productive of sulphydryl or abnormally sensitive thereto.

The first possibility has but little experimental or observational support. Further, it yields no satisfactory explanation of the nature, etiology and diverse manifestations of tumors.

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24. Warburg, O.; Wind, F., and Negelein, E.: *Metabolism of Tumors in the Body*, J. General Physiol. **8**:519, 1928.

25. Hopkins, F. G., and Dixon, M.: *On Glutathione: II. A Thermostable Oxidation-Reduction System*, J. Biol. Chem. **54**:527, 1922.

26. Mueller, J. H.: *The Effect of Oxidation of Filtrates of a Chicken Sarcoma (Chicken Tumor I-Rous)*, J. Exper. Med. **48**:343, 1928.

27. Harde, E.: *The Influence of an Acid Reaction on the Virus of the Chicken Sarcoma (Rous) and Its Importance in the Experiments of Dr. Gye*, J. Trop. Med. **29**:159, 1926.

28. Tunnicliffe, H. E.: *Glutathione: Reactions Between the Tissues and the Oxidized Dipeptide*, Biochem. J. **19**:199, 1925.



The increased concentration of sulphhydryl in living tumor tissue might be taken as evidence of an inherent trend to overproduction. Opposed to this is the fact that, by and large, cell proliferation is confined to the tumor and does not spread to contiguous tissue. If sulphhydryl were being produced in abnormally high concentrations, it might be expected that adjacent tissues would respond hereto<sup>29</sup> with growth by cell division; and this does not occur. Further, there is the fact that in growing animals the concentration of sulphhydryl is highest in the youngest and gradually declines with age, as growth by cell division subsides.<sup>30</sup> Finally, it is a fact that in regions where active normal growth by cell reproduction is taking place, the concentration of sulphhydryl is high.<sup>11</sup> From this, it follows that the high concentration of sulphhydryl in malignant tissue is due to the fact that the cells are proliferating cells. The idea that tumor cells are abnormally productive of the stimulating group is unsustained.

The increased reducing power of the blood<sup>14</sup> and the increase in the neutral sulphur fraction of the total sulphur of the urine<sup>13</sup> might also be taken as evidence of an overproduction of sulphhydryl by the malignant growth. But it can also be assumed that malignancy is an expression of a distortion of the cellular response to sulphhydryl. It is, therefore, not unreasonable to suppose that there is inherent in those who are subject to malignant growths a tendency to a basic distortion of sulphur metabolism. From this, it follows that the picture in the blood and the urine may be but an expression of this perversion rather than an expression of an overproduction of sulphhydryl from the tumor as such.

This interpretation implies no neglect of the fact that other diseases produce a similar gross picture. On the other hand, it is well known that different causes may produce the same physiologic effect. This arises from the fact that the end-results of reaction to diverse stimuli are limited by the biochemical mechanisms concerned in the general metabolic processes. Similarity in type of response is no proof of identity in the initiating agent. Since this statement is founded on fundamentals, it is valid until disproved by adequate investigation.

The available evidence having proved insufficient to establish whether or not malignant growth is a consequence of an abnormal productivity of sulphhydryl by the tumor-forming cells, it remains to examine the

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29. Hammett (footnote 12). Gurwitsch, A.: *Das Problem der Zellteilung physiologisch Betrachtet*, Monograph aus der gesamtgeschichte der Physiologie der Pflanzen und der Tiere, no. 11, Berlin, Julius Springer, 1926.

30. Thompson, J. W., and Voegtlin, C.: *Glutathione Content of Normal Animals*, J. Biol. Chem. **70**:793, 1926. Murray, H. A., Jr.: *Physiological Ontogeny: A. Chicken Embryos: IX. The Iodine Reaction for the Quantitative Determination of Glutathione in the Tissues as a Function of Age*, J. General Physiol. **9**:621, 1926.

alternative, that the malignant growth is based on an abnormal sensitivity of the tumor-forming cells to sulphhydryl.

This, perhaps, can best be done from the point of view of the more important etiologic concepts of malignancy.

Biologically, the etiologic factors of malignancy, as presented by Ewing<sup>31</sup> and Loeb,<sup>32</sup> are separable into two groups, the constitutional and the acquired.

All persons during the course of years are subjected to one or more of the tumor-inciting agents. But all persons do not incur malignant growths. The only possible conclusion is that susceptibility to the disease is constitutionally determined.

Countless clinical records attest the fact that the inception of many malignant growths is an antecedent irritation. Since the constitutional make-up is inborn and present before the reception of the tumor-evolving agent, it is clear that the initiation of malignancy depends on the application of an adequate stimulus. The constitutional factors provide the ground on which the acquired factors exert their influence. Only the combination results in malignancy.

The following classification provides a useful basis for analysis:

- A. Constitutional factors
  - 1. Heredity
  - 2. Cell autonomy
  - 3. Internal secretion
  - 4. Embryonal (congenital)
- B. Acquired factors
  - 1. Irritation
    - (a) Mechanical
    - (b) Physiologic
    - (c) Chemical
    - (d) Parasitic

*Heredity.*—The difference between persons who bear tumors and those who do not is a constitutionally determined difference in the nuclear activities related to cell proliferation. This difference expressed in malignancy is an inheritable characteristic. The work of Loeb,<sup>33</sup> Slye,<sup>34</sup> Little<sup>35</sup> and others can yield no other conclusion.

31. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922.

32. Loeb, L.: *Causes and Definition of Cancer*, *Am. J. M. Sc.* **159**:781, 1920.

33. Loeb, L.: *Heredity and Internal Secretion in the Etiology of Cancer*. Internat. Conference on Cancer, London, 1928, p. 48.

34. Slye, M.: *The Relation of Cancer to Heredity with Regard to the Communication of President C. C. Little of the University of Michigan*, *J. Cancer Research* **12**:83, 1928.

35. Little, C. C.: *Evidence that Cancer Is not a Simple Mendelian Recessive*, *J. Cancer Research* **12**:30, 1928.

My experimental work justifies the belief that sulphhydryl is specifically essential to the nuclear processes of cell division.<sup>12</sup> As is well known, these are integrated by the chromosomes, and the chromosomes are the determinants of the inherited characteristics. Therefore, the factor of heredity would be a determinant of the level of nuclear response to sulphhydryl.

These considerations and the known correlation between malignancy and sulphhydryl lead to the conclusion that the inheritability of malignancy is conditioned, if not determined, by an inbred shift in nuclear reactivity to sulphhydryl. The data are thus consistent with the assumption that malignancy results from an abnormal sensitivity of the tumor-producing cells to sulphhydryl.

*Cell Autonomy.*—Many side issues are included in the consideration of this constitutional factor as discussed by Ewing.<sup>31</sup> They all boil down to the question of the inherent proliferative properties of the cancer cell, and the relation of the tissue environment thereto.

Some preliminary definition is necessary.

The inherent proliferative energy of cells has nothing to do with the total possible number of cells producible, for this is limitless, as the studies of Carrel<sup>36</sup> and Woodruff<sup>37</sup> prove. Nor has it anything directly to do with the rate of formation of new cells, since this is largely controlled by environmental factors.<sup>38</sup> Its sole property is the determination of the nuclear threshold of response to proliferative stimulation. This is a matter of constitutional makeup or heredity and is related to the sensitivity to sulphhydryl, as shown in preceding paragraphs. The concept is thus in agreement with the assumption of the greater sensitivity of the malignant cell to sulphhydryl.

The other chief item in the bracket for cell autonomy is the question of restraints on growth. These can be considered under three headings: architectural, cytologic and chemical.

The histologic point of view has been adequately discussed by Reimann in the aforementioned paper, in which he shows that the diverse architecture of malignant growths is essentially a consequence of the diverse anatomic and physiologic environments in which the proliferation of cells takes place. The architecture, then, is no index of the inherent proliferative capacity of the growth. It merely shows what the growth can do in the particular environment in which it occurs. Hence it is only of supplementary significance in etiology.

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36. Carrel, A.: Tissue Culture and Cell Physiology, *Physiol. Rev.* **4**:1, 1924.

37. Woodruff, L. L.: Eleven Thousand Generations of Paramecium, *Quart. Rev. Biol.* **1**:436, 1926.

38. Gurwitsch (footnote 29, second reference).

As discussed by Reimann, the cytologic status resolves itself into the question of the relation of cell size to rate of malignant growth, and the stage of cell development at the time of proliferation in its bearing on the type of tumor produced. The latter is essentially an architectural matter; but the former is directly relatable to the interpretation of malignancy in terms of sulphydryl.

It has been found that in a cell population where growth by increase in cell number and growth by increase in cell size are taking place simultaneously, small cell size is associated with increased rate of cell division.<sup>39</sup> And the pathologists have observed that small cell size is generally indicative of a high degree of malignancy as established by subsequent history. Thus, cytologically, in both normal and pathologic material, cell size is a rough index of the extent of the autonomous restraint on growth.

The parallelism demonstrates that the phenomena of cell size in malignancy are on the same biologic basis as are those of normal growth by increase in cell number, when and if the masking influences of environmental factors are properly accounted for. On the basis of the experimental data cited, it is clear that this relationship is further evidence in support of the assumption under discussion.

As to the matter of autonomous chemical restraints on growth it is obvious that such exist. The work of Carrel<sup>36</sup> and others with tissue cultures proves that unlimited proliferation of cells will not occur unless the products of the growth reaction are repeatedly removed from the scene. There are, thus, restrictive and stimulative factors of cell division through which equilibrium is maintained in the normal person. From what has gone before and from purely chemical considerations based on the law of mass action, it can be asserted that cell proliferation is regulated by a chemical equilibrium in which sulphydryl is the key group. From this, it follows that the autonomous chemical restraints on growth by increase in cell number are, in all probability, products of the oxidation of sulphydryl.<sup>12</sup>

The assumption that malignancy is the result of an unusual sensitivity of the tumor-producing cells to sulphydryl is supported by this concept. For, on the basis of the equilibrium hypothesis it is clear that if the threshold of response to inhibition is raised, as it surely is in malignancy, then the threshold of response to stimulation must be lowered, else no unusual proliferation of cells would take place. In other words, the point of equilibrium is shifted toward the sensitivity to R-SH side of the equation.

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39. Hammett, F. S.: Cell Division and Cell Growth in Size, Protoplasma, to be published.

This is sufficient and all that is necessary to indicate that the major concepts in the bracket of cell autonomy in malignancy are interpretable in terms of sensitivity to sulphydryl.

*Internal Secretion.*—Next in the order of importance of the constitutional factors of malignancy is internal secretion. At present, the evidence justifies the inclusion of but one incretory organ in the group. This is the ovary. The others have no proved influence, save the thyroid gland.

The influence of ovarian incretory activity is a purely constitutional factor, since the ebbing and flowing of this is a normal phenomenon of the female. In the etiology of tumor, it is the most important constitutional factor next to heredity and cell autonomy, since the majority of malignant growths in the female are traceable thereto.

At present there is no evidence justifying the designation of the thyroid gland as a purely constitutional factor in the sense that shifts in its level of activity within usual limits are etiologic factors in malignancy. It is only of demonstrable significance when it has acquired an abnormal level of functional activity. This is usually a consequence of exogenous stimulation.<sup>40</sup> Hence the rôle of the organ in malignancy is logically to be considered under the heading of acquired factors, until it is shown that an etiologic relationship is present within the usual range of the functional level.

Loeb<sup>41</sup> conclusively demonstrated the fact which Cori<sup>42</sup> and others confirmed—that ovarian incretory activity is of great significance in the production of mammary carcinoma in mice. In fact, Loeb stated that the realization of the hereditary tendency to cancer presupposes the activity of the internal secretion of the ovary. Without this cooperation no cancer can originate.

Statistical records show that malignant growths occur most frequently in women in just those organs subjected to periodic ovarian stimulation.

In the aforementioned paper, Reimann described, with absorbing interest, the histologic changes that take place in the human breast under ovarian stimulation during the recurrent menstrual cycles. He wrote, "In the normal breast there is a constant reciprocal growth and recession of epithelium and connective tissue." Biochemically, this means that the breast is periodically subjected to a flooding with cellu-

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40. Hammett, F. S.: Thyroid and Growth, *Quart. Rev. Biol.*, to be published.

41. Loeb, L.: Quantitative Relations Between the Factors Causing Cancer and the Rapidity and Frequency of the Resulting Cancerous Transformation, *J. Cancer Research* 8:274, 1924.

42. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas in Mice, *J. Exper. Med.* 45:983, 1927.

lar disintegrative products. From the work of Bierich and Kalle<sup>43</sup> it is known that catabolic processes similar to this are liberative of sulphhydryl from the protein-bound unreactive state to the free condition in which characteristic action is possible.

Now all breasts are subjected to this stimulus to the proliferation of cells, but all breasts do not respond by a cancerous overgrowth. In most, the cellular regeneration stops short of this point. The valid implication is that in those in which cancer does develop the threshold of sensitivity to sulphhydryl is lower than usual. The facts, as a whole, are consistent with this hypothesis, and permit an extension of its application to those other tumor-producing organs that are subject to periodic ovarian stimulation.

There is no space here to go into Loeb's<sup>41</sup> rigidly critical analysis of the etiology of cancer of the breast. Those who are interested enough to study his admirable paper will find in the sulphhydryl hypothesis an explanation of the principles therein set forth.

*Embryonic Rests.*—Cohnheim's dictum that cells retaining embryonal characteristics are significant agents in the etiology of tumor is too well attested by comparative observations to be questioned. The usual conception is that these so-called embryonal rests are the result of a congenital distortion of differential development. This is probable in such cases as Albrecht's hamartoma and the like. On the other hand, it is also possible that the majority of cases derive from one or more lines of cells in which embryonal characteristics, so far as proliferative potentialities are concerned, are retained because of hereditary forces. These lines can be considered as minority contributors to the mass building of tissues and organs and thus they provide foci from which malignant growths may arise on adequate stimulation.

This conception, which as a possibility has no genetic negation, provides a more satisfactory explanation for most of the tumors classed as embryonal than does that of congenital distortion. Both ideas, however, stress the fact of the origin of tumors from cells retaining embryonic characteristics of cell proliferation. Experimental evidence supporting the assumption is had from the serologic studies of Gruskin.<sup>44</sup> This worker apparently demonstrated a homologous relationship between embryonic and malignant cells by amboceptor and antigen reactions with mammalian embryonic epithelium and connective tissue.

The studies of Müller<sup>45</sup> lend support to this view. He found a close histologic correspondence between epithelial regeneration in wounds

43. Bierich, R., and Kalle, K.: Untersuchungen über das Zustandekommen der bösartigen Geschwülste, Ztschr. f. physiol. Chem. **175**:292, 1928.

44. Gruskin, B.: A Serum Test for the Diagnosis of Cancer Based on a New Theory of Etiology, Am. J. M. Sc. **177**:476, 1929.

45. Müller, H.: Die histologische Uebereinstimmung zwischen Epithelregeneration und Krebsbildung, Ztschr. f. Krebsforsch. **28**:383, 1929.

and cancerous organization. Yet in the one case only normal repair occurs, while in the other the cells proliferate to malignancy. There is, thus, a fundamental difference in their reaction to stimulation, which is interpretable only on the basis of the foregoing hypothesis. Müller's observations are also in line with those of Carrel on tissue cultured fibroblasts. For this latter worker reports that no histologic, only metabolic, differences are ascertainable.

The concept is fittingly interpretable from the point of view of a low threshold to sulphydryl. For it has been found in this institute, in working with chick embryos, that the regions of most active growth by increase in cell number are most stimulated to proliferation of cells by sulphydryl. That is to say, the more embryonal the cells are, as evidenced by their more rapid rate of division,<sup>46</sup> the more sensitive they are to sulphydryl.

The fact that all malignant growths are expressions of but one fundamental biologic phenomenon, i.e., cell proliferation, makes it imperative that any interpretation of the basic etiology of tumor be also founded on a single principle.

The foregoing analysis of the constitutional factors shows this condition to have been satisfied. From it comes the conclusion that the potentiality for malignancy lies in the hereditary determination of lines of cells retaining the embryonic characteristic of a heightened sensitivity to the essential cell proliferation stimulus, sulphydryl.

The chief phenomena of malignancy fit in with this concept.

There is no evidence, save in rare instances, that the cells of a malignant growth possess the functional properties of the organ from which they originate. This is significant. It means that if the ontogenetically mature cells of the organ become tumor-producing cells they dedifferentiate in the process; or it means that the growths arise from cells of hereditarily determined embryonic characteristics, and hence, because of their low ontogenetic level, cannot go on to normal differentiation.

The dedifferentiation can be rejected on the grounds of the work of Lewis and Lewis<sup>47</sup> with tissue cultures. On the basis of the alternative implication, the phenomenon is consistent with the premise of this discussion.

The fact of metastasis is evidence for the idea discussed by Reimann from the point of view of stroma reaction, that tumor cells are not

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46. Minot, C. S.: *The Problem of Age, Growth, and Death*, New York, G. P. Putnam's Sons, 1908.

47. Lewis, W. H., and Lewis, M. R.: *Behavior of Cells in Tissue Cultures*, in Cowdry, E. V.: *General Cytology*, Chicago, University of Chicago Press, 1924, pp. 383-448.

foreign cells. Further, the cells of the metastases increase in number, but those of the diverse supporting tissue rarely give evidence of tumor-like cell multiplication. These facts indicate that the metastatic cells are lines of body cells in which the embryonic characteristic of a low threshold to the stimulus of proliferation is retained. Further, the fact that the liver and the lymph nodes are common seats of metastasizing growths is significant in that the former is the organ of the highest natural sulphhydryl content<sup>30</sup> and the latter are foci of cell multiplication. Thus, the phenomenon fits in with, and is support for, the conclusion that has been drawn.

Now it is not unreasonable to suppose that lines of cells with this low threshold may separate at any one of the several earliest stages of the development of the egg before the organic patterns have made their appearance. This may be conceived of as occurring, in some cases, before cellular differentiation has proceeded far, perhaps not much beyond the period of the three germ layers. In others, the separation may take place at the time of the formation of the organ anlage.

In the first case, a general dissemination of the potentially malignant cells would be predicted according to the germ layer in which they have their origin. In the second, the potentiality would be restricted to the organ from the anlage of which the cells derived. If these considerations are correct, it follows that both a general and a local predisposition to tumor on adequate stimulation are to be expected. Since such predispositions do occur, as exemplified in the first and third cases cited by Reimann, it is clear that the facts fit the theory, and further support is had for the interpretation of the constitutional factors of malignancy in preceding paragraphs.

The question may properly be raised, if the potentiality for malignancy lies in hereditarily determined lines of cells of low threshold to sulphhydryl, why do the majority of tumors fail to arise until long after normal growth by increase in cell number has ceased? Surely, since in the early stages there is an adequate concentration for the multiplication of normally constituted cells, there is more than enough for the multiplication of the potentially tumor-producing cells of high sensitivity.

Now the thesis has been developed from experimental observations that growth by increase in cell number is a self-regulated chemical process in which sulphhydryl is the key group. This is the essential stimulus. The inhabitant is taken to be an as yet unidentified product of the oxidation thereof, arising in the natural course of the chemical processes concerned in cell division.<sup>12</sup> Since normal cells numerically predominate during the developmental period as in the adult, their mass production of the inhibitant of proliferation is conceivably the means of holding in check the minority of low-threshold, tumor-potential cells.



As development proceeds, the concentration of sulphhydryl decreases concomitantly with growth by increase in cell number,<sup>48</sup> while the concentration of the chemical inhibitants presumably increases. Thus, less and less favorable conditions for the expression of the tumor-producing potentiality develop, until at adulthood the concentration of sulphhydryl is below the stimulative level. Until and unless this is increased to an adequate concentration, malignancy does not develop. This is the interpretation of latency.

*Anemia of Malignancy.*—The anemia that occasionally accompanies certain types of malignant disease is also explicable in terms of sulphhydryl. Here, however, the apparent exceptions make the interpretation more suggestive than conclusive. On the other hand, it is worth a thought.

The explanation is based on two facts. The first is that sulphhydryl is essential to cell proliferation.<sup>12</sup> The second is that as tumors grow larger the sulphhydryl of the rest of the body declines.<sup>17</sup> The implication, then, is that tumor growth lowers the concentration of sulphhydryl in the bone-marrow and thus the formation of red cells is dampened. Consistent with, but not proof for, the idea is the fact that liver, which stimulates erythropoiesis, has a high sulphhydryl content,<sup>30</sup> and the fact that the concentrated active agent from liver has a high cystine content.<sup>49</sup>

*Irritation: Mechanical Injury or Trauma.*—It is now possible to turn to the discussion of the acquired factors of malignancy without which no tumor is possible. Those which have been proved to be effective properly come under the heading of irritation, when this term is used in the broad sense of Verworn. That is to say, mechanical, physiologic, chemical and parasitic actions are able to produce a state of irritation that, in a constitutionally prepared person, results in malignancy. This state of irritation, however, is but the expression of an underlying disruption of a previously existing chemical equilibrium.

In the light of this fact, one is in a position to examine the data available with respect to the various inciting agents and see whether they fit the concept that sulphhydryl is a necessary participant in the development of malignant disease.

No one will question that many malignant growths are traceable to an antecedent contusion. Nor will any one question that cellular disintegration or autolysis follows such injury. Therefore, since Bierich and Kalle<sup>43</sup> have shown that previously bound sulphhydryl is liberated in free form on tissue autolysis, it can be postulated that an increased concentration of this group arises on traumatization.

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48. Mueller (footnote 26). Thompson and Voegtlin (footnote 30, first reference).

49. Looney, J. M.: The Analysis of Liver Extract, J. Biol. Chem. **78**:11, 1928.

Direct and indirect evidence, as well as inferential, is at hand. Reiche<sup>50</sup> found that tissue autolysates favor mitosis. Haberlandt<sup>4</sup> observed stimulation of cell division after injury. Giroud and Bulliard<sup>51</sup> noted an association between sulphydryl concentration in the skin and keratinization, while Lightbody and Lewis<sup>52</sup> confirmed this principle on dietary grounds. Significantly, Carnot and Terris<sup>53</sup> got remarkable healing of cutaneous wounds by extracts of proliferating skin. Finally, I have consistently obtained a marked intensification of the nitroprusside test for sulphydryl on injury of root-tips, either by crushing or by scratching.<sup>11</sup>

All these facts lead to the one conclusion that trauma liberates sulphydryl, which then acts as a stimulus to cell proliferation. The fact that trauma is frequently productive of malignancy is, thus, strong support for the theory being developed in this paper.

*Physiologic Irritation.*—This discussion is purposely limited to data derived from experimental and clinical observation. Speculation without such a basis is unwarranted under the present circumstances. Because of this, consideration of the physiologic factors of malignancy is restricted to the internal secretion of the thyroid gland. No other physiologic activity gives even a suggestion of being an acquired factor in the development of malignant disease. Even in the case of the secretion of the thyroid gland the evidence is circumstantial. The observations, however, are sufficiently numerous, and the explanation, therefore, is sufficiently consistent with the whole background, to justify the postulation of a relationship as a generalization.

Dercum,<sup>54</sup> in a stimulating analysis, reviewed the data on the clinical association between thyroid activity and malignancy. The sum and substance of his collected observations is that malignant disease is infrequent, if not rare, in persons suffering from hyperthyroidism.

This negative correlation might be predicted from the known facts relative to thyroid function and sulphydryl lability. For it is well known that the metabolic rate is regulated by the level of thyroid activity, and that when this is increased, the oxidative processes of the body are

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50. Reiche, H.: Ueber Auslösung von Zellteilung durch Injektion von Gewebssäften und Zelltrümmern, *Ztschr. f. Bot.* **16**:241, 1924.

51. Giroud, A., and Bulliard, H.: Glutathione et kératine, *Compt. rend. Soc. de biol.* **98**:500, 1928.

52. Lightbody, H. D., and Lewis, H. B.: The Metabolism of Sulfur: XV. The Relation of the Protein and Cystine Content of the Diet to the Growth of Hair in the White Rat, *J. Biol. Chem.* **82**:485, 1929.

53. Carnot, P., and Terris, E.: Sur la cicatrisation de plaies cutanées par les extraits d'embryons de peau régénérée, *Compt. rend. Soc. de biol.* **95**:655, 1926.

54. Dercum, F. X.: The Biological Interpretation of Malignancy, *Cancer J.* **2**:97, 1925.

enhanced.<sup>40</sup> Further, it is a fact that the sulphhydryl group is exquisitely sensitive to oxidizing agents.<sup>25</sup> Hence, other things being equal, the chance for the development in a person with hyperthyroidism of a sulphhydryl concentration adequate to produce malignant cell proliferation is limited. Other supportive argument could be made, but this is sufficient to establish the consistency of the phenomenon with the general thesis.

*Chemical Irritation.*—Malignant cell proliferation is also directly initiated by chemical substances, particularly those related to the tarry by-products of the distillation of coal and petroleum. Apparently, two factors are responsible here: (1) repeated irritation, which may be produced either by friction or by irritating substances in the tars, and (2) the presence of the tarry products themselves.

When such agents give rise to truly metastasizing malignant growths, a constitutional predisposition is undoubted. In many cases, however, the growths do not progress after the removal of the exciting agent and may even regress. They also fail to recur when surgically extirpated if the subject comes in no further contact with the stimulus to cell proliferation, even though similar irritation is produced. In these cases, a constitutional predisposition is questionable. Rather is the original growth attributable to the presentation to the irritated cells of an extraordinary concentration of cell proliferation stimulus from tar constituents over and above that liberated by the injury. This is the logical deduction from the pertinent data. Biologically, the principle is fundamentally correct, for it has been found that the experimental increase in the normal cell multiplication stimulus, sulphhydryl, causes an acceleration of normal cell division.<sup>12</sup>

The residues of the distillation of both coal<sup>55</sup> and petroleum<sup>56</sup> are characterized by significant percentages of mercaptans and sulphides; the oils themselves, of course, likewise.

In view of all that has gone before, it is reasonable to assume that the tar and allied cancers are but the proliferative reaction of irritated tissues to a concentration of sulphhydryl above that necessary for normal cell division repair.

Sustaining evidence for this conclusion is had. It has been found that tumors cannot be produced experimentally by any and every tar, but that only certain products are effective. This is associable with the fact that petroleum from different localities contains widely different percent-

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55. Stadnikov, G.; Gravilov, N., and Rakovskii, V.: Desulfurization of Cresols and Acid Fractions of Various Coal Tars, *Brennstoff. Chem.* **7**:65, 1926. Mailhe, A.: Sulfur Compounds in Coal Tar, *J. usines gaz.* **41**:209, 1921.

56. Day, D. T.: *Handbook of the Petroleum Industry*, New York, John Wiley & Sons, 1922.

ages of labile sulphur compounds, ranging from negligible to significant amounts.<sup>57</sup>

The picture is consistent with the general concept of the relation of sulphydryl to malignancy.

The foregoing interpretation might be objected to on the observation of Murphy and Landsteiner<sup>58</sup> that a sarcoma produced in the chicken by the combined injection of tar and embryonic tissue is transplantable through succeeding generations. But so are other, spontaneously occurring chicken tumors.<sup>59</sup> This latter fact would indicate that there is a constitutionally determined ground for the development of tumor in the fowl susceptible to stimulation by appropriate agencies.

In the spontaneous tumors transmissible by filtrates and desiccates, this agent is, according to Murphy,<sup>60</sup> enzymic in nature and, hence, endogenous or constitutionally determined. Transmissibility, as well as transplantability, indicates that the activating agent is produced by the tumor cells themselves. The essential similarity of this with sulphydryl in its reactions has already been pointed out.

In the case of the tar tumor, the irritating agent is, in all probability, the labile sulphur, as discussed. Its nontransmissibility by filtrates or desiccates<sup>61</sup> should cause no wonder. In this case, an exogenous stimulus starts off a malignant growth in a constitutionally disposed animal, which is naturally transplantable into other similarly constitutionally disposed animals, but not transmissible since the irritating agent is not endogenous.

*Parasitic Irritation.*—The brilliant studies of Fibiger<sup>62</sup> with animals, and of Smith<sup>63</sup> with plants, make necessary the inclusion of parasitic organisms in the group of incitants to malignant growth.

In the case of *Spiroptera carcinomata*, indirect evidence brings the reaction in line with the general concept. The provocative organisms

57. Redwood, B.: Treatise on Petroleum, Philadelphia, J. B. Lippincott Company, 1922.

58. Murphy, J. B., and Landsteiner, K.: Experimental Production and Transmission of Tar Sarcomas in Chickens, J. Exper. Med. **41**:807, 1925.

59. Rous, P., and Lange, L. B.: The Characters of a Third Transplantable Chicken Tumor Due to a Filtrable Cause: A Sarcoma of Intracanalicular Pattern, J. Exper. Med. **18**:651, 1913.

60. Murphy, J. B.: The Nature of the Filtrable Agent in Chicken Tumors, Report of the International Conference on Cancer, London, 1928.

61. Sturm, E., and Murphy, J. B.: Further Observations on an Experimentally Produced Sarcoma of the Chicken, J. Exper. Med. **47**:493, 1928.

62. Fibiger, J.: On Spiroptera Carcinomata and Their Relation to True Malignant Tumors: With Some Remarks on Cancer Age, J. Cancer Research **4**: 367, 1919.

63. Smith, E. F.: Studies on the Crown-Gall of Plants: Its Relation to Human Cancer, J. Cancer Research **1**:231, 1916.

produce eggs in huge numbers. Shearer<sup>64</sup> found that on fertilization the concentration of free sulphhydryl in the eggs of *Echinoderm* increases markedly. This reaction is probably general. Further, it is well known that nematodes have great regenerative capacities. Since this is a phenomenon of cell division presumably dependent on sulphhydryl, it follows that here is a possible additional source of supply of the stimulus to cell multiplication. The idea, then, is that through production of eggs and fertilization of them, and the chemical stimuli of regeneration, *Spiroptera* provides a concentration of sulphhydryl adequate to stimulate an abnormal proliferation of cells in a ground prepared by the inflammatory processes and constitutionally inclined to a pathologic response.

In the case of *Bacillus tumefaciens*, the data are also meager. Direct knowledge is had only of the first step in the reaction: that the organism excites inflammatory processes which, in constitutionally prepared persons, go on to malignancy.<sup>65</sup> Now, inflammation is the result of an injury,<sup>66</sup> and, as stated earlier, injury of plant root tissues results in liberation of free sulphhydryl. Correlating these facts leads to the conclusion that the phenomenon is interpretable in terms of the generalization. It would be decidedly worth while to see whether or not *B. tumefaciens* possesses any specific type of sulphur metabolism that would be correlatable with its tumor-producing properties.

Studies with other parasites have thus far yielded no sure conclusion.<sup>31</sup> There are certain facts, however, which are suggestive in the light of the present interpretation. It is known that mercaptans and hydrogen sulphide are produced in the large intestine by the bacterial decomposition of protein food residues.<sup>13</sup> Miss Margaret Sharpe, working in this institute, found that both hydrogen sulphide and its disodium salt are effective stimulants of reproduction in *Paramecium caudatum*. Thus, there is present in the colon the chemical stimulus for a proliferation of cells as an acquired factor from bacterial activity. This is present in varying concentration. From this, it is obvious that conditions are frequently favorable for the development of malignancy in constitutionally susceptible persons. I am inclined to believe that this is often a potent factor in the genesis of rectal carcinoma. Contributory would be constipation, with its attendant accumulation of bacterial by-products and consequent irritation. The

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64. Shearer, C.: Oxidation Processes of the Echinoderm Egg During Fertilization, Proc. Roy. Soc., London **93**:213, 1922.

65. Levin, I., and Levine, M.: Malignancy of the Crown-Gall and Its Analogy to Animal Cancer, J. Cancer Research **5**:243, 1920.

66. Rivera, V.: E necessaria la ferita del tessuto per la produzione di tumori da *B. tumefaciens* su vegetali? Boll. Accad. pugliese sc. **1**:1, 1926.

fact that about 60 per cent of the cases of constipation are proctogenic<sup>67</sup> supports this idea.

From this analysis of the mechanisms of the constitutional and the acquired factors in malignancy, it is clear that they are all reducible to a common basis. Thus the condition as outlined on an earlier page is satisfied, i. e., that any interpretation of the basis of tumor genesis must be founded on a single principle, since all malignancy is but the expression of one fundamental biologic phenomenon, namely, the proliferation of cells.

Further, the data in this bracket are support for the idea developed during the analysis of the constitutional factors, that the cells which proliferate to malignancy are abnormally sensitive to sulphydryl.

#### SUMMARY AND CONCLUSION

This synthesis has been based on the biologic principle that any satisfactory interpretation of malignant growths must be founded on a knowledge of the chemical stimulus to growth by increase in cell number.

The first step was a description of the experimental work leading to a demonstration that the sulphydryl group is the essential stimulus to multiplication of cells in healthy material. Direct transference of this observation to tumor tissue is allowable on the basis of Baker's<sup>68</sup> report that glutathione, a sulphydryl-containing compound, is stimulative of a proliferation of cells in tissue cultures of sarcomatous fibroblasts.

The next step was an examination of the available reports with respect to sulphur metabolism in general and sulphydryl in particular in tumor-bearing persons and tumor tissue. From this, it was seen that the correlative data consistently support the idea of an inter-relationship between sulphydryl and malignancy.

The third step was an examination of the etiologic concepts of malignancy for the purpose of seeing whether or not they could be lined up on a common basis. From the known facts, the thesis was developed that malignancy, in general, is a product of a combination of constitutional and acquired factors. An analysis of these showed that their influence is interpretable in terms of sulphydryl.

The chief manifestations of malignancy were also tested against this concept and found to be sustaining thereof.

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67. Reimann, S. P.: *The Pathological Physiology of Surgical Diseases* by Prof. Dr. Franz Rost, Philadelphia, P. Blakiston's Son & Company, 1923.

68. Baker, L. E.: *The Chemical Nature of the Substances Required for Cell Multiplications: II. Action of Glutathione, Hemoglobin, and Ash of Liver on the Growth of Fibroblasts*, *J. Exper. Med.* **49**:163, 1929.

From all this the generalization has developed that the potentiality for malignancy lies in the hereditary determination of lines of cells retaining the embryonic characteristic of a heightened sensitivity to the essential stimulus to proliferation of cells, sulphhydryl, and that the development of malignancy depends on the presentation to the potentially tumor-producing cells of an adequate concentration of this chemical group.

I am quite willing to admit that this interpretation is possibly not the last word in the apparently complex problem of malignant disease. On the other hand, it does suffice to bring some order out of a previously existing chaos. Its validity, of course, rests on the soundness of the biologic principles involved.

# A REVIEW OF THE PLEURAL AND PULMONARY LESIONS IN TWENTY-EIGHT FATAL CASES OF ACTIVE RHEUMATIC FEVER\*

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Clinically, lesions of the respiratory system have received considerable attention in rheumatic fever, as pleurisy and even pneumonia have been said to be common manifestations of this disease.<sup>1</sup> Nevertheless, the nature of these lesions is somewhat ill defined; the number of pathologic studies that have been brought to bear on them is small, and there are certain fundamental questions about the lesions which remain unanswered, such as the extent to which they are specific manifestations of rheumatic fever. In this disease, the respiratory system may be the seat of a variety of injuries. For example, besides pleurisy and bronchopneumonia, so often found in rheumatic fever, almost all the fatal cases exhibited pulmonary manifestations of failing cardiac function, frequently with the presence of transudate fluid in the chest cavities associated with varying degrees of pulmonary atelectasis, passive congestion, pulmonary edema, infarction, etc. Our primary purpose in this paper is to record the outstanding pulmonary changes observed in a series of fatal, active cases of rheumatic fever and, in our analysis of them, an attempt will be made to isolate those few lesions that we believe represent specific manifestations of this obscure disease.

Recent work embracing such a study of pathologic material in rheumatic fever includes that of Thayer,<sup>2</sup> who reviewed a series of twenty-five fatal cases of active rheumatic fever from the necropsy series of the Johns Hopkins Hospital. The author recorded pulmonary changes, but apparently he had not studied these in detail. All his cases showed pulmonary evidences of myocardial insufficiency. Terminal

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\* Submitted for publication, Jan. 4, 1929.

\* From the Ayer Clinical Laboratory of the Pennsylvania Hospital.

\* A more comprehensive review of the material reported in this paper is included in the 1928 Alvarenga Prize Essay of the College of Physicians and Surgeons, Philadelphia.

1. The literature on this subject has been reviewed in a recent article by Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine* 7:383, 1928.

2. Thayer, W. S.: Notes on Acute Rheumatic Diseases of the Heart, *Bull. Johns Hopkins Hosp.* 36:99, 1925.



pneumonia or bronchopneumonia was noted in 40 per cent. The pleural lesions were not recorded.

A large series of cases of rheumatic fever in which necropsies were made was studied by Pappenheimer and von Glahn,<sup>3</sup> who paid particular attention to the vascular lesions. They did not offer detailed studies of the lungs, but reported the presence of lesions, in a small percentage of the cases, involving peripheral arteries, arterioles and capillaries in the pulmonary, as well as in the systemic, circulation.

Others<sup>4</sup> who have described the pulmonary changes in cases of rheumatic fever have found the most prominent lesion to be a diffuse "pneumonitis," consisting of an acute interstitial or perivascular, nonsuppurative type of inflammation, and have been struck with the resemblance between this lesion and the classic rheumatic lesion of the myocardium.

#### MATERIAL

The material on which our study is based was obtained from the necropsy series of the Pennsylvania Hospital. This series totaled, at the time, about 3,600 cases. In selecting cases for study, only those were included in which death had occurred during an active stage of the disease. The criterion of activity was the finding of Aschoff bodies in the myocardium (found in 85 per cent of the cases) together with endocardial and valvular lesions and also pericardial lesions. Cases in which there was an extensive ulcerative endocarditis associated with the presence of large numbers of bacteria were not included. In a few, however, tiny ulcerations were present on the cardiac valves together with typical rheumatic vegetations and, from three of these, hemolytic or anhemolytic streptococci were isolated.

Fourteen of the twenty-eight cases had occurred since 1922. These we had had the opportunity of studying first hand. The remaining fourteen were selected from the older series. Information concerning them was obtained from the protocols but more especially from our studies of the available tissue that had been preserved.

#### RESULTS

The different lesions encountered will be considered under a number of different headings.

*Pleurisy.*—Rheumatic pleurisy has been said to occur in from 5 to 10 per cent of clinical cases of rheumatic fever, usually accompanying rheumatic pericarditis and, as a rule, indicating a severe rheumatic infection. It does not seem to have been clearly defined, however; perhaps

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3. Pappenheimer, A. M., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, *J. M. Research* **44**:489, 1924. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* **2**:235, 1926.

4. Eiman, J., and Gouley, B. A.: Rheumatic Pneumonitis, *Tr. Path. Soc., Philadelphia, Arch. Path.* **5**:556 (March) 1928. Naish, A. E.: The Rheumatic Lung, *Lancet* **2**:10 (July 7) 1928.

because one is loathe to accept the mere presence of fibrinous pleurisy or the accumulation of pleural fluid in this disease as an indication of a pleurisy that is essentially rheumatic.

In our series of cases, many of which represented that severe and fulminating form of rheumatic fever which occurs in children, active pericarditis was present at necropsy in 75 per cent, and active pleurisy in 64 per cent of the cases.

Three cases with active pleurisy, in which typical bronchopneumonia was present, have not been included in the discussion. Many others with diffuse focal hemorrhages in the lung gave a picture that might be classified as acute hemorrhagic bronchopneumonia, although the degree to which this lesion is related to the pleural one has not been determined. However, the characteristic feature of the latter group was that the pleural lesion was more extensive than that usually found in association with the common types of acute hemorrhagic lobular pneumonia. Furthermore, it was always nonsuppurative, and in none of the cases in which bacteriologic studies were made, were organisms demonstrated in direct association with it.

The type of nonsuppurative pleurisy that has been designated by many authors as rheumatic pleurisy bears a close resemblance to the pericardial lesion. In the material furnished by our cases, it showed the following characteristics:

**Gross Appearances:** As an early manifestation, small, focal collections of pinhead-sized petechial hemorrhages, similar to the epicardial or pericardial hemorrhages so frequently found in this disease, appeared on the visceral pleural surface, either with or without the presence of hemorrhagic lesions in the underlying pulmonary tissue.

A later stage, and this proved to be by far the commonest manifestation, was the appearance of fibrinous exudate on the pleural surfaces. This was noted in half the cases, and in most instances there was also an accumulation of fluid in the pleural cavity. Undoubtedly, many factors contributed to the accumulation of the fluid in the pleural cavity as a terminal event, but our studies pointed to a relatively specific type of injury to the pleura as playing a leading rôle in this. Certainly, the amount of fluid exudate, and its character, are closely related to the degree of inflammation of the pleura. Pleural fluid was present in eighteen cases of the series; in five, it exhibited the essential characteristics of a transudate and was associated with ascites and edema of the extremities; but, in the remaining thirteen, it was the accompaniment of a frank pleurisy with effusion. We shall limit our descriptions to these cases, which we believe presented the type of pleurisy peculiar to rheumatic fever.

The fluid will be described later.

The lungs were usually found moderately compressed, particularly in their dependent portions, and over these areas the pleura appeared slightly opaque. Pleural vessels and lymphatics were frequently dilated and opaque, and unusually prominent, often outlining individual lobules with a "chicken wire" effect. Closer inspection sometimes revealed a fine, thin film of fibrin covering certain areas of the lung. As the process advanced, and particularly in those cases in which an

excess of fluid had accumulated, the surfaces sometimes appeared opaque and roughened, with strings of fibrin traversing the cavities from atelectatic lung or pericardial sac to the chest wall. Three of the cases in the series presented this picture.

Subsequently, organization of the fibrinous adhesions occurred, probably with the absorption of varying amounts of fluid, and this process was sometimes encountered in all stages. A common picture was the combination of fibrin and loose fibrous tissue giving rise to fairly soft, white adhesions, which enclosed small, loculated areas of fluid, generally involving the medial, posterior and inferior surfaces of the lower lobes to a greater or less degree.

As with many inflammations of the pleura, eventually fibrous adhesions were left as landmarks of the previous lesion. The mere finding of such adhesions in our series of cases, of course, gave us little information as to their origin; we paid scant attention to them, therefore, apart from noting that they occurred in over 60 per cent of the cases. However, in none of these cases, which included many in which there had been a history of repeated attacks of rheumatic fever, did we find a really thickened or hyalinized pleura analogous to that of the older stages of tuberculous pleurisy.

**Pleural Fluid:** The type of effusion which has been so frequently encountered in the pleural cavities in the course of rheumatic fever has been described by Swift<sup>5</sup> and others.<sup>6</sup> In our series of cases, the pleural fluid varied in appearance from almost that of a transudate to that of a frank exudate, probably depending on the degree of inflammation of the pleura. As a rule, this fluid was straw colored, clear or slightly turbid; in a small number of instances, particularly in young children, it was definitely hemorrhagic. We have referred to the fact that the fibrinogen content was high. This was roughly demonstrated in the ability of the fluid to clot on standing. As a rule, however, fibrin showed itself by the presence of actual flecks or floating strings of white material, a glance at the open chest sometimes revealing the presence of small particles or, in some instances, huge masses floating or deposited on the pleural surfaces. As most of these particles were too large to penetrate the lumen of the ordinary trocar, they did not appear in the usual specimen obtained by aspiration. The cytologic content of the fluid was subject to great variations; we found, as a rule, however, a predominance of mesothelial cells and lymphocytes with a scarcity of polymorphonuclear cells.

In the many bacteriologic studies that we made, we failed to demonstrate bacteria in this fluid.

**Histologic Studies of the Pleural Lesion:** We confined our histologic studies to a few of the cases that we believed presented most characteristically the pleural inflammation peculiar to this disease. Here, again, the picture resembled that of rheumatic pericarditis. In the earlier stages, we found marked swelling and a uniform increase in the size of the lining mesothelial cells, so that they almost resembled columnar epithelium. One of the features of this metaplasia was the size and character assumed by the cell nucleus. It became large, pale and vesicular, almost foamy in texture, and was dotted with multiple, basophilic nucleoli (fig. 1). Scattered among these swollen cells were some showing

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5. Swift, H. E.: Rheumatic Fever, Nelson's Loose-Leaf Living Medicine 1:418, 1920.

6. Bezançon, F., and Weil, M. P.: La cortico-pleurite rhumatismale, Ann. de méd. 19:184, 1926.

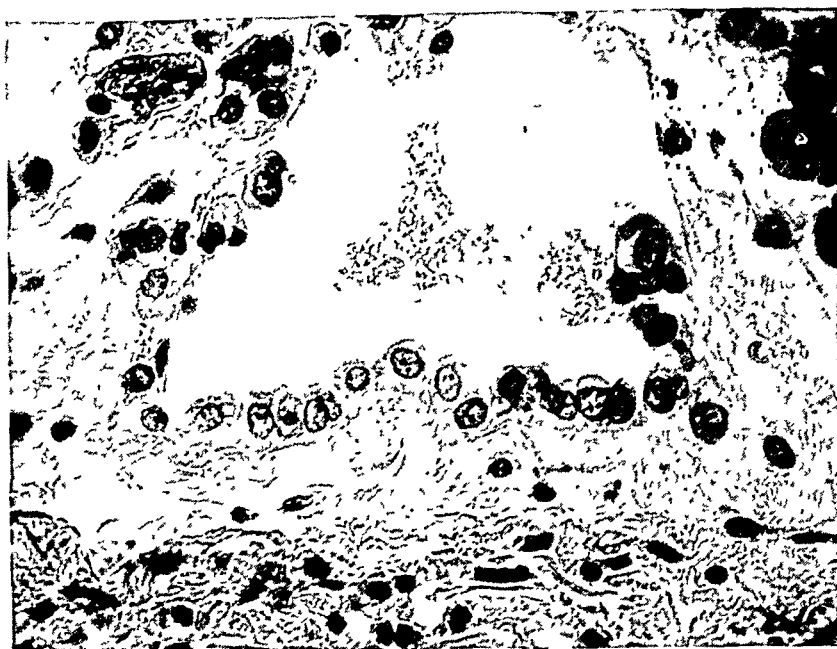


Fig. 1 (case 24).—A small portion of the pleural surface on which the lining endothelial cells show swelling and other characteristic changes. Many of them have formed multinucleated giant cells and have split away from the basement membrane.

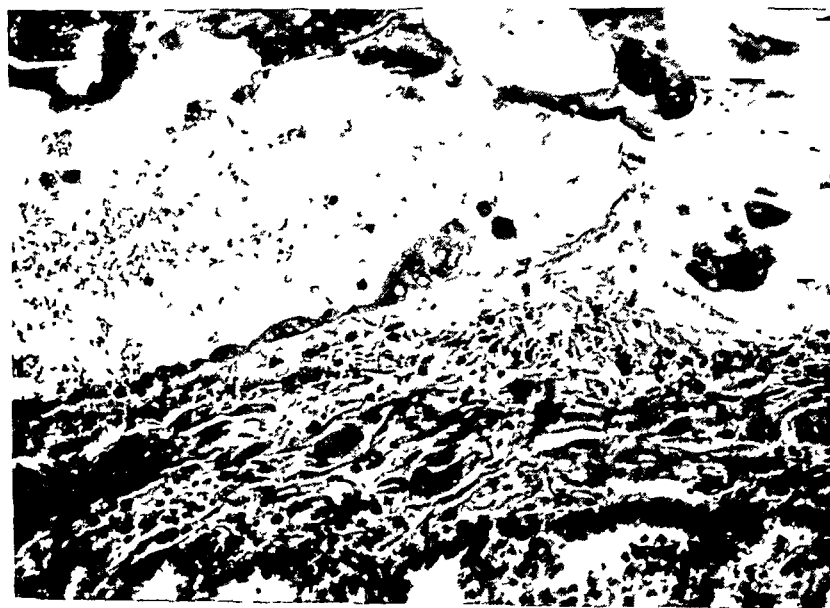


Fig. 2 (case 24).—A pleural surface showing endothelial swelling with formation of giant cells and desquamation. At the right, a mass of deeply stained fibrin covers the surface. Evidences of inflammation are present in the subpleural layers.

evidences of degeneration with vacuolization of the cytoplasm and shrinking and pyknosis of the nuclei, as well as some that showed nuclear division. Many of the cells became oval or spherical, forming large, multinuclear giant cells at this stage (fig. 2) and split away from their basement membrane (figs. 1 and 2), leaving a denuded surface, to which shreds of fibrin became attached (figs. 2 and 3). Associated with these changes of the lining mesothelium, particularly in the denuded areas, the subpleural tissues exhibited a low grade inflammatory reaction characterized by moderate edema and the appearance of scattered lymphoid cells, occasional polymorphonuclear cells, plasma cells, mast cells, eosinophils, etc. (fig. 3). It was not unusual to find in these areas large mononuclear cells in which the cytoplasm stained red with methyl-green-pyronin. New capillaries were formed in these subpleural areas. They often appeared as small ducts owing to the fact that their lining endothelium also sometimes showed vary-

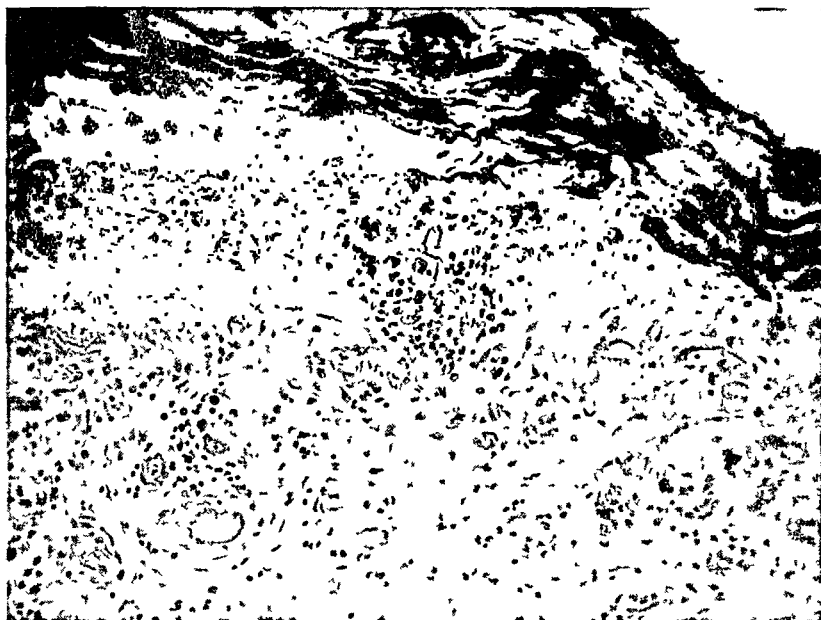


Fig. 3 (case 24).—A subpleural space. To the denuded surface, masses of fibrin have become attached, beneath which there is a wide layer of granulation tissue, rich in capillaries. Many of these show swelling of their lining endothelium, notably a vessel in the lower left hand corner. Scattered diffusely or in perivascular locations are many lymphoid, plasma and wandering cells.

ing degrees of swelling (fig. 3); occasionally they were thrombosed and sometimes showed hyalinization of their walls.

The older pleural lesions gave rise to a variety of pictures. The subpleural spaces in some areas were replaced by a thick layer of granulation tissue, which was the site of an extensive inflammatory reaction. In other areas, in which moderate protection of the originally denuded surface had occurred, in the form of a thin hyalinized membrane probably derived from fibrin, the subpleural inflammatory changes were not nearly so pronounced. We sometimes found the surface in such an area thrown into folds, directly beneath which were fairly compact groups of large cells (fig. 4), recalling in some measure the histologic

picture of the now familiar lesion of the endocardium in the wall of the left auricle which was described by MacCallum<sup>7</sup> and von Glahn.<sup>8</sup>

Another striking picture which was noted in several cases with effusion was little, finger-like projections or mesothelium-lined villi on the pleural surface (fig. 5).

In general, however, neither the gross nor the histologic picture of this lesion was sufficiently specific to differentiate it clearly from that seen in a variety of types of pleural inflammation, except perhaps for the paucity of polymorphonuclear cells and the consistent absence of bacteria. Furthermore, apart from the fact that the injury appeared to be an acute or subacute inflammation, we know little of its true nature,



Fig. 4 (case 24).—A pleural surface from which the endothelial lining has desquamated and on which it has been replaced by a thin hyalinized membrane. A characteristic type of endothelial cell proliferation may be seen in the subpleural layers.

although we were impressed with the fact that one of its earliest demonstrable manifestations was in the lining mesothelium. The inflammatory processes which involved this mesothelium seemed to be essentially those of swelling, metaplasia, formation of giant cells, desquamation and cell death. Associated with this process, particularly after the pleural surface had been denuded of its lining, there was an intense,

7. MacCallum, W. G.: Rheumatic Lesions of the Left Auricle of the Heart, *Bull. Johns Hopkins Hosp.* **35**:324, 1924; Rheumatism, The Harrington Lecture, *J. A. M. A.* **84**: 1545 (May 23) 1925.

8. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, *Am. J. Path.* **2**:1, 1926.

rather characteristic chronic inflammation of the subpleural tissues and it is interesting to recall in this connection that French authors applied the term "cortico-pleurite" to rheumatic pleurisy in an endeavor to emphasize that there is a characteristic involvement of both the pleura and the subpleural layers. The growth of new capillaries into the subpleural space was marked, and they, too, presented swelling of the lining endothelium and also degenerative changes, such as hyalinization of their walls.

All these changes sometimes were and sometimes were not associated with underlying lesions in the lung proper. We were unable to assume that they represented the surface manifestations of a constant



Fig. 5 (case 7).—Pleura and subpleural space. Endothelium lined villi project from the surface. Many new capillaries may be seen in the underlying spaces.

lesion within the lung. The phenomena reminded us rather of the pleural lesion of tuberculosis, which may or may not accompany an extensive intrapulmonic lesion.

Another question that concerns the nature of this pleural lesion and one which has been often raised is whether or not it represents an extension from the pericardial lesion. Many authors have called attention to the high incidence of pleural involvement in rheumatic pericarditis, although it has also been said that the pleurisy may develop without the carditis. In our series of cases, we observed four instances of active fibrinous pleurisy occurring in the absence of an active pericarditis. It was evident, none the less, that the pericardial and pleural lesions were

closely related by virtue of their proximity and by virtue of the fact that they appeared in the same general type of tissue; but, from the data at hand, we feel that the paths of infection cannot as yet be satisfactorily traced, for we do not know the nature of the infection. Nevertheless we are inclined to believe with Mosler<sup>9</sup> and others that serous surfaces are favorite sites of injury in rheumatic fever. Indeed, besides that of the synovial membranes, inflammation of the peritoneum and of the meninges has been noted. It is even conceivable that, in the thoracic cavity, one has an exaggerated local manifestation of a more generalized process for which local factors, such as the cardiac and respiratory movements, may be responsible—a possibility that is also reflected in the subdiaphragmatic peritonitis or perihepatitis to which attention has been called in this disease.

*Vascular Lesions.*—We reviewed the literature dealing with these lesions in a previous article.<sup>1</sup> It is interesting to compare our observations with those that have been recently described.

**Main Pulmonary Artery:** Atheroma of the pulmonary artery and its larger branches is a familiar observation in cases of long-standing pulmonary congestion, and especially in mitral stenosis. It was noted in two of our cases, in each of which both mitral and pulmonic endocarditis was present.

Histologic studies of the base of the main pulmonary artery were made in six cases. In one (table 1, no. 1), a case in which atheroma of the pulmonary artery had been noted grossly, microscopic lesions were found in the wall similar to those that have been described in the aorta in this disease.<sup>8</sup> The medial coat of the pulmonary artery was the seat of a destructive lesion, with splitting of the elastic fibers and an extensive deposition of scar tissue. Typical Aschoff bodies were also found in the adventitial layers of the base of the pulmonary artery and of the aorta.<sup>10</sup> (Kugel and Epstein<sup>11</sup> have recently reported the presence of similar lesions in five of a series of twenty-four active cases of rheumatic infections of the heart.)

**Pulmonary Arteries of Moderate Size:** Grossly, we were unable to detect any changes in these vessels other than occasional thrombosis. Histologically, fairly extensive changes were detected in four cases and slight changes in twelve others.

In the branches in which the lumen measures from 2 to 3 mm. in diameter, the lesion conformed rather with the type seen in the aorta or main pulmonary artery. The histologic picture was not striking, consisting, as it did, of slight metaplasia or proliferation of intimal cells together with thickening of the medial coat. Furthermore, it did not seem to be particularly specific, recalling

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9. Mosler, E.: Ueber rheumatische Entzündung der serösen Häute (sogenannte Polyserositis rheumatica), Berl. klin. Wchnschr. **47**:277, 1910.

10. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, Tr. Path. Soc., Philadelphia, Arch. Path. **3**:352 (Feb.) 1927.

11. Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, Arch. Path. **6**:247 (Aug.) 1928.



the changes that have been described as occurring in the peripheral blood vessels in a variety of acute infections,<sup>12</sup> such as influenza, etc.

**Arterioles:** The lesions in the arterioles appeared to be the most prominent, although it may have been only because the changes in the arterioles were more easily detected than those in vessels of larger caliber. This was particularly true of vessels in which the lumen was about the size of a glomerulus. As a rule, we found either many vessels involved or none at all, and such changes, both recent and old, were found in about 40 per cent of our cases. Focal hemorrhages within the lung or hemorrhagic bronchopneumonia invariably accompanied this lesion. Histologically, the process was well described by von Glahn and Pappenheimer (1926).<sup>3</sup> It seemed to be essentially a panarteritis, although the most striking changes manifested themselves in the intima and the adventitia. Primarily, the lining endothelium became swollen and vacuolated, so that the intima often

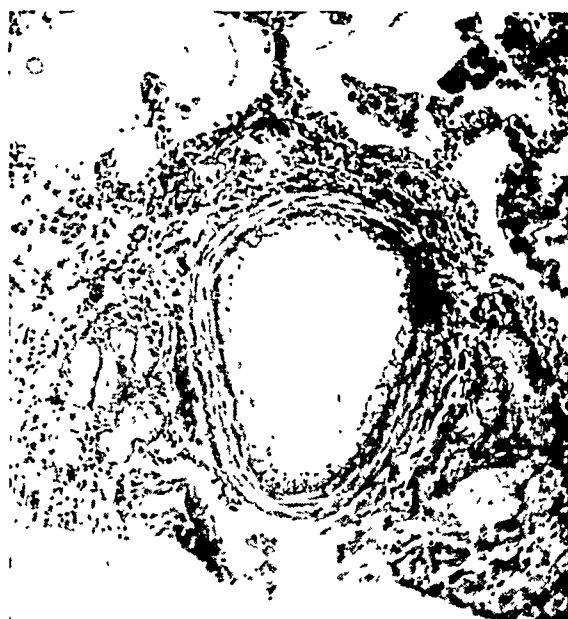


Fig. 6 (case 23).—A small pulmonary artery. The intimal cells are vacuolated and raised away from the elastic membrane. There is marked congestion of the perivascular vessels, with some perivascular accumulations of cells.

appeared, raised away from its basement membrane by delicate strands (figs. 6 and 7). A more pronounced and perhaps a later stage of this process was the formation on the intimal surface of a layer of foamy or vacuolated cells. In the media, we sometimes also found vacuoles associated with distortion of the muscle fibers and accompanying evidences of injury and death of cells, as shown by the presence of pyknotic and shrunken nuclei. Associated with the early stage of intimal metaplasia and proliferation there was sometimes, in the adventitia or in a perivascular zone, a corresponding response to damage of the tissue, characterized by marked dilatation and hyperemia of the perivascular capillaries (fig. 6). Accompanying this hyperemia were other evidences of local

12. Wiesel, J., and Löwy, R.: Die Erkrankungen der peripheren Gefäße bei akuter und chronischer Krieslauf insuffizienz, *Wien. klin. Wchnschr.* **32**:1083, 1919.

injury, such as hemorrhage and the presence of fibrin and a few scattered wandering cells. However, such perivascular accumulations of wandering cells were not, as a rule, extensive in actual numbers of cells. In character, they recalled, for the most part, those which we described as occurring in association with the pleural lesion; rarely did we see many polymorphonuclear cells; occasionally, we found cells in this location in which the cytoplasm stained red with the Unna-Pappenheim stain, but we failed to find groups of cells that recalled the classic Aschoff nodule of the myocardium. The occurrence of thrombi within the lumina of injured vessels was frequently noted. Frank obliterative endarteritis was also noted, but it was generally found with some other lesion of the lung, such as atelectasis, which might well be responsible for involutionary changes in the vessels.



Fig. 7 (case 23).—A pulmonary arteriole with intimal changes.

Reparative or end-stages of the vascular lesions were manifested by slight thickening and hyalinization of the intima and thickening and scarring of the medial coat, together with perivascular fibrosis.

Veins: We did not detect any noteworthy changes in the walls of the veins.

Other lesions involving the lung proper which were encountered may be listed as follows:

*Pulmonary Atelectasis.*—Although varying in degree, this was an almost constant observation in the dependent portions of the lung, particularly of the left lung. A number of factors probably played a rôle in bringing about this phenomenon, such as fluid in the pleural cavities; the enlarged pericardial sac generally associated with pericarditis, and bronchitis, which may inhibit pulmonary aeration. Pericardial enlargement, however, proved to be a particularly important contributing factor.

We cannot overemphasize the relatively enormous size which the pericardium sometimes attained in these cases, due either to cardiac enlargement, to an effusion or to fibrinous pericarditis with associated edema of the sac wall, to an old obliterative pericarditis or to a combination of some of these processes. Pulmonary compression from enlargement of the pericardial sac was present in at least two thirds of the cases.

Histologically, the changes in the atelectatic areas did not prove to be remarkable, except that in the pulmonary vessels in certain lungs which had undergone long-standing compression, the degree of endarteritis was sometimes extreme, often resulting in a marked diminution of the lumen. We also found various stages of perivascular inflammation and fibrosis. We believe that such changes were distinct from the specific vascular changes described and that they were essentially involutionary as a result of prolonged pulmonary compression. In the atelectatic areas, the bronchi also became, at times, the seat of an intense chronic inflammatory reaction.

*Bronchopneumonia or Lobular Pneumonia.*—Considerable discussion has arisen as to whether a specific type of pneumonia exists in rheumatic fever.<sup>13</sup> One of the difficulties in reaching an agreement seems to be that of terminology or definition. In our series, examples of the classic bronchopneumonia occurring in a variety of acute infections, such as measles and influenza, appeared to be relatively uncommon, but a rather unusual hemorrhagic lesion that may be logically classed as a "pneumonia" seemed to be not at all infrequent. This latter lesion was represented by multiple hemorrhagic foci sometimes widely scattered throughout the lung substance. It was a particularly common observation in fatal cases in children, and has been described, according to Naish,<sup>4</sup> by Pichon and Lardé-Arthés.

In this condition, the pleural surfaces presented a mottled appearance due to small, generally round and definitely firm areas of subpleural hemorrhage, averaging from 0.5 to 1.5 cm. in diameter, and limited, as a rule, to individual lobules (fig. 8). Similar hemorrhagic foci, more or less lobular in distribution, were also found scattered throughout the lung substance as round, dark red nodules.

Histologically, these small hemorrhagic areas appeared as compact masses of red cells and fibrin within individual alveoli and atriae (fig. 9). A small portion of a lobule, a whole lobule or several lobules were occasionally involved, but, as a rule, the areas were focal rather than confluent. The picture suggested actual intra-alveolar hemorrhage and one of the outstanding characteristics of the material that collected in the alveoli was the amount of fibrin, so that in late stages, as the result of its organization, groups of alveoli and even bronchioles became filled with a cast of loose fibrous tissue. We studied these areas of focal hemorrhage with bacterial stains, and in none of them were we able to demon-

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13. Rabinowitz, M. A.: Rheumatic Pneumonia, J. A. M. A. **87**:142 (July 17) 1926.

strate bacteria in the interstitial tissue or within the alveoli. In practically all the cases, however, moderate degrees of bronchitis or bronchiolitis were present and bacteria were easily demonstrable within the lumina of terminal bronchi, associated with definite inflammation of the mucous and submucous coats.<sup>14</sup>

Associated with this hemorrhagic lesion and probably representing a later stage, intra-alveolar exudate, fairly rich in polymorphonuclear cells, was found in four of the cases. The picture was characterized grossly by patches of confluent lobules showing gray hepatization. Here, again, however, we experienced difficulty in demonstrating bacteria and in only one did we succeed in demonstrating them within the alveoli; the age of the process, however, may have been responsible for their absence.

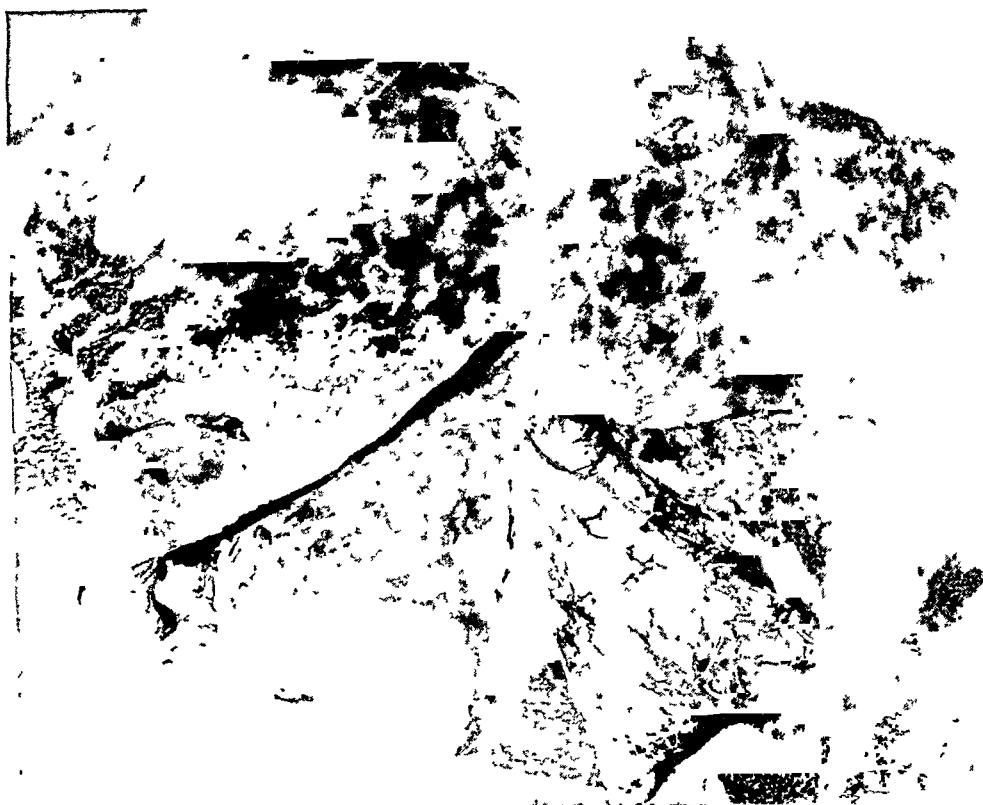


Fig. 8 (case 26).—The lungs viewed posteriorly. Hemorrhagic foci are well shown in the upper lobes and their relationship to individual lobules can also be discerned.

Although the nature of this characteristic lesion was not clear, the picture suggested that of an acute hemorrhagic lobular pneumonia. A

14. Cultures were taken from four of the lungs showing the hemorrhagic lesions. From one of these, we did not obtain any growth at all; from two, we obtained small numbers of *Streptococcus viridans* and from another a scanty growth of anhemolytic streptococci. We have not stressed the significance of these results, for we do not know whether the organisms were actually obtained from the lung tissue proper or from the lumen of a terminal bronchiole. However, the bacteriologic observations were not quite in accord with those usually encountered in hemorrhagic lobular pneumonia.

number of factors, however, may have influenced this picture; the lesion may have been the result of an injury to the vessel walls, such as the lesions just described, or it may have been the result of a pneumonia in a lung that was already the seat of marked circulatory stasis.

*Bronchitis and Bronchiolitis.*—Bronchitis or bronchiolitis was an almost constant observation, associated, no doubt, with the ever present circulatory stasis.

*Chronic Passive Congestion.*—Pulmonary congestion was present in some degree in every case. Nothing particularly remarkable was noted about this picture except perhaps the fact that frank pulmonary edema was uncommon. Most of the lungs were “dry” rather than

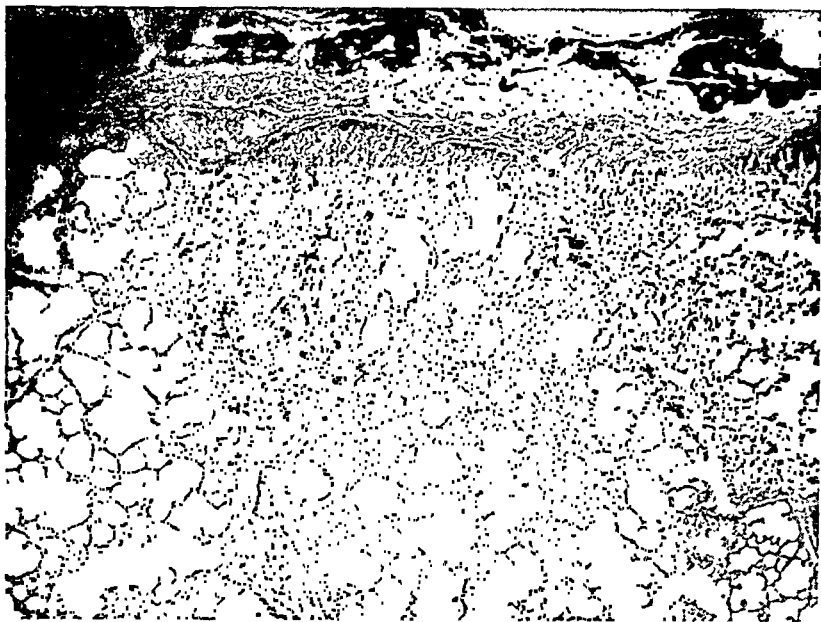


Fig. 9 (case 24).—A typical histologic view of the hemorrhagic lesion shown grossly in figure 8, including a peripheral lobule and the adjacent pleura. One may note the lobular distribution of the exudate, which consists largely of red cells.

“wet.” The picture was often complicated by varying degrees of pulmonary atelectasis in the dependent parts of the lungs.

*Thrombosis of Pulmonary Arteries and Pulmonary Infarction.*—Thrombi were found in pulmonary arteries of considerable size with relative frequency, occurring in several instances without the presence of infarcts. Gross pulmonary infarcts were present in six cases, or 20 per cent of the series. In five of these cases, pulmonary infarction was associated with the accumulation of an excess of fluid in the pleural cavity on the affected side.

*Summary of Observations.*—The observations in the series have been summarized in the accompanying table, in which the cases have been ranged according to the ages of the patients. The cardiac lesions are also tabulated in a way to show the degree of myocardial, endocardial and pericardial involvement. The close association between fibrinous pericarditis and fibrinous pleurisy is shown by this table. The cases showing hemorrhagic lobular pneumonia have been listed in a separate column. It may be noted that this lesion is sharply restricted to patients under 20 years of age.

*Cardiac and Pulmonary Lesions Encountered in the Series of Cases of Fatal Rheumatic Fever*

Case*	Age	Cardiac Lesions					Pulmonary Lesions						
		Myocarditis—Aschoff Bodies	Endocarditis†				Fibrinous Pleurisy	Pleural Fluid, Cc.		Vascular Lesions	Hemorrhagic Foci	Broncho-pneumonia with Gray Hepatization	Gross Infarcts
			T	P	M	A		Right	Left				
24	6	++++	+	..	+	+	++++	0	0	+++	+++	0	0
6	8	+	..	..	+	+	+++	150	50	0	++	+	0
16	10	++	..	..	+	+	+++	300	300	0	+	0	0
4	13	++	..	..	+	+	+++	600	30	0	+	±	0
15	14	++	..	..	+	+	++	0	0	0	+	0	0
21	14	+++	+	..	+	+	±	50	50	+	(old)	0	0
26	14	0	..	..	+	+	0	50	50	0	++	0	0
27	14	±	+	..	+	+	0	2,000	200	±	±	±	++
19	15	±	..	..	+	+	0	75	100	0	+	0	0
22	15	+	+	..	+	+	+++	500	800	±	+	0	+
23	15	++	..	..	+	+	0	0	0	++	++	0	0
5	16	++	..	..	+	+	+++	0	200	±	(old)	+	0
10	16	+	..	..	+	+	+++	200	200	0	+	0	0
11	16	0	..	..	+	+	+++	50	20	+	(old)	0	0
9	17	+	+	..	+	..	++	1,800	100	0	(old)	+	++
2	19	0	+	..	+	+	±	1,000	250	+	(old)	+	+++
7	19	+++	..	..	+	+	+++	230	20	+	+	0	0
20	19	+	+	..	+	+	+	250	150	+	(old)	++	0
28	21	+++	+	+	+	+	+	200	150	+	(old)	++	0
12	22	±	+	..	+	+	+++	200	0	+	(old)	0	0
17	22	++	..	..	+	+	+++	200	200	+	(old)	0	0
8	23	±	+	+	+	+	+++	600	0	0	0	0	0
14	24	0	..	..	+	+	+	500	75	0	0	0	0
18	21	+++	+	+	+	+	+	1,500	800	±	0	0	+
13	25	±	+	..	+	..	+	0	0	±	0	0	+
25	25	+	+	..	+	+	+	200	20	(old)	0	0	0
3	28	±	+	+	+	+	+	400	100	+	(old)	0	0
1	32	+++	+	..	+	..	+	1,000	0	0	0	0	0

\* The cases are ranged in order of the ages of the patients.

† The most extensive lesions are designated as +++.

‡ T P M A indicate tricuspid, pulmonic, mitral and aortic valves.

CONCLUSIONS

We have listed the pleural and pulmonary observations in a series of twenty-eight necropsies performed on patients dying in active stages of rheumatic fever.

Primarily, we have been impressed with the relative frequency of pleurisy in this series, active inflammation of the pleura having been detected in about half the cases. Although difficult to define, the pleurisy described represents, we believe, a specific manifestation of the rheumatic infection and is distinguishable from that encountered in the

usual bacterial infections of the respiratory tract by the nonsuppurative character of the exudate and by our inability to demonstrate bacteria in association with it. This lesion, which resembles rheumatic pericarditis, is probably more common than is generally thought to be the case. It is, as a rule, less extensive than pericarditis, and associated with far less serious consequences. It manifests itself in a number of different forms but is generally accompanied by the accumulation of pleural fluid, which may be hemorrhagic, particularly in young children, and is nearly always rich in fibrin. It bears a close resemblance to tuberculous lesions of the pleura, but differs from this last infection in that it does not reveal a thickened, hyalinized pleura as an end-stage.

We have also studied the lesions that occur in and about the pulmonary vessels, and in this study have confirmed the observations of von Glahn and Pappenheimer (1926).<sup>3</sup> Rheumatic fever is not the only disease that gives rise to changes of this general type, particularly in peripheral vessels, for we recognize the arteritis of several acute infections. Nevertheless, we are impressed with the fact that such lesions are prominent in rheumatic fever and that they appear to be manifestations of a generalized infectious process.

Terminal lobular pneumonia, in its ordinarily accepted sense or in the sense in which it occurs following measles or influenza, proved to be fairly uncommon in our series, but we noted, particularly in those cases occurring in childhood, the presence of focal or hemorrhagic lobular pneumonia exhibiting certain atypical features as described. Evidence has not accumulated to suggest that this lesion is a specific manifestation of rheumatic fever, although it seems to be a fairly constant observation in the disease.

# CONGENITAL STENOSIS OF THE THIRD PORTION OF THE DUODENUM WITH ACUTE OCCLUSION AND RUPTURE OF STOMACH \*

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The case here reported is of interest from a clinical as well as from a pathologic point of view: from the former, in that the patient had had, throughout life, symptoms of intermittent high intestinal obstruction, which led finally by acute occlusion and rupture of the stomach to death; and from the latter, in that the occlusion was in the inferior horizontal portion of the duodenum exactly at the site where arterio-mesenteric occlusion of the duodenum occurs. In fact, the condition was at first regarded as such; closer examination, however, revealed a marked stenosis of the duodenum, the lumen being partially occluded by a membranous septum with an opening about 4 mm. in diameter. The wall of the duodenum oral to the site of obstruction was distinctly hypertrophied, as was also the wall of the stomach. The rupture of the stomach was on the anterior wall near the cardia and was presumably the result of overdistention from the injudicious administration of enemas. The combination of unusual features makes this case unique.

## REPORT OF CASE

*Clinical History.*—The patient was a girl 8 years of age. The father stated that she had had attacks of nausea and vomiting, abdominal distention, pain in the upper part of the abdomen and constipation for several years. At times, the child would vomit material which had been eaten days or even weeks before. Enemas usually gave relief. On March 8, 1928, the child ate a lunch consisting mainly of a thick vegetable soup of cabbage, corn and spinach. At about 4 p. m. she complained of abdominal distention and pain. The mother then gave her an enema of soap suds and castor oil by the gravity method. None of the first enema was returned; so a second, third and fourth were given, with apparently no appreciable amount of fluid being returned in any instance. An enema bag of 2-quart size was used; conservatively, from 4 to 6 quarts of fluid were probably injected. The patient commenced vomiting a greenish fluid. Her condition became rapidly worse. A physician was called and the child was removed to the South Shore Hospital. By this time there was extreme cyanosis; the abdomen was greatly distended, tympanitic and of boardlike rigidity. A diagnosis of pneumoperitoneum was made. At 8:30 p. m., while being prepared for operation, the patient expired.

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\* Submitted for publication, April 8, 1929.

\* From the Department of Pathology, University of Chicago.

\* Read at the Chicago Pathological Society, April 9, 1928.



*Necropsy.*—The postmortem examination was made one hour later. The child was well developed and well nourished. Rigor mortis was not present. Cyanosis was extremely marked. The abdomen was tremendously distended and tympanitic, and when it was opened, air under great pressure escaped. The abdominal cavity contained approximately 1.5 liters of a soapy, oily fluid, together with cabbage and spinach leaves and fragments of corn. Smears from this revealed only yeasts and a few gram-positive cocci. At a point from 1 to 2 cm. from the cardiac orifice of the stomach was a tear about 1.5 cm. in diameter, through which vegetable leaves protruded. The stomach was markedly distended by a soapy, oily fluid, and contained vegetable leaves and debris, six olive seeds and two glass beads.



Fig. 1.—The abdominal viscera after the small and large intestines were inflated with air through a cannula inserted into the rectum.

To the left of the esophageal hiatus and extending into the mediastinum was a hernia-like pouch into which vegetable leaves were packed.

The duodenum was greatly dilated and the wall distinctly thickened to a point where the mesentery crossed the inferior horizontal portion. From here on, the small intestine and colon were relatively collapsed and free from fluid. A noteworthy feature was the presence of countless air bubbles between the layers of the mesentery, particularly of the mesocolon and mesosigmoid. The intestines contained practically no fecal material. Air introduced into the rectum by a tube, passed easily throughout the bowel up to the place where the obstruction occurred (figs. 1 and 2). When the mesentery was lifted, the air passed into the remainder of the duodenum.

The other significant observations were: marked distention of the right side of the heart with dark blood, small ecchymoses in the pleurae of both lungs and acute generalized passive hyperemia.

*Description of Fixed Specimen.*—The specimen, as shown in figures 1 and 2, consisted of all the abdominal organs removed and fixed in toto.

The stomach was distended and, except for a tear near the cardiac orifice, presented nothing unusual on external examination. There was a slight narrow-



Fig. 2.—The abdominal viscera showing the enlargement of the duodenum.

ing corresponding to the pyloric ring. The duodenum was immensely dilated and its wall appeared firm. The dilatation extended up to a point where the inferior horizontal portion of the duodenum was crossed by the root of the mesentery; beyond this point, the duodenum, as well as the jejunum and ileum, appeared normal. The stomach and duodenum were opened by scissors, the former on the ventral surface about 3 cm from and parallel to the greater curvature, the latter along its convex margin. In the fornix of the stomach, the plicae were scarce;

in the corpus, they were less prominent than is usual. The following measurements were taken: the wall was 2 mm. thick about the fornix, from 3 to 6 mm. in the prepyloric region and 8 mm. thick 1 cm. oral to the pyloric ring. The circumference of the stomach, 5 cm. oral to the pyloric ring, was 13 cm.; at the pyloric ring, it was 4.5 cm.

The wall of the duodenum was thickened and its mucosa appeared to be stretched. Three centimeters distal to the pyloric ring, the circumference of the duodenum was 11.5 cm., and the wall was 2 mm. thick. An iris-like membranous diaphragm narrowed the lumen of the duodenum at a point 18 cm. from the

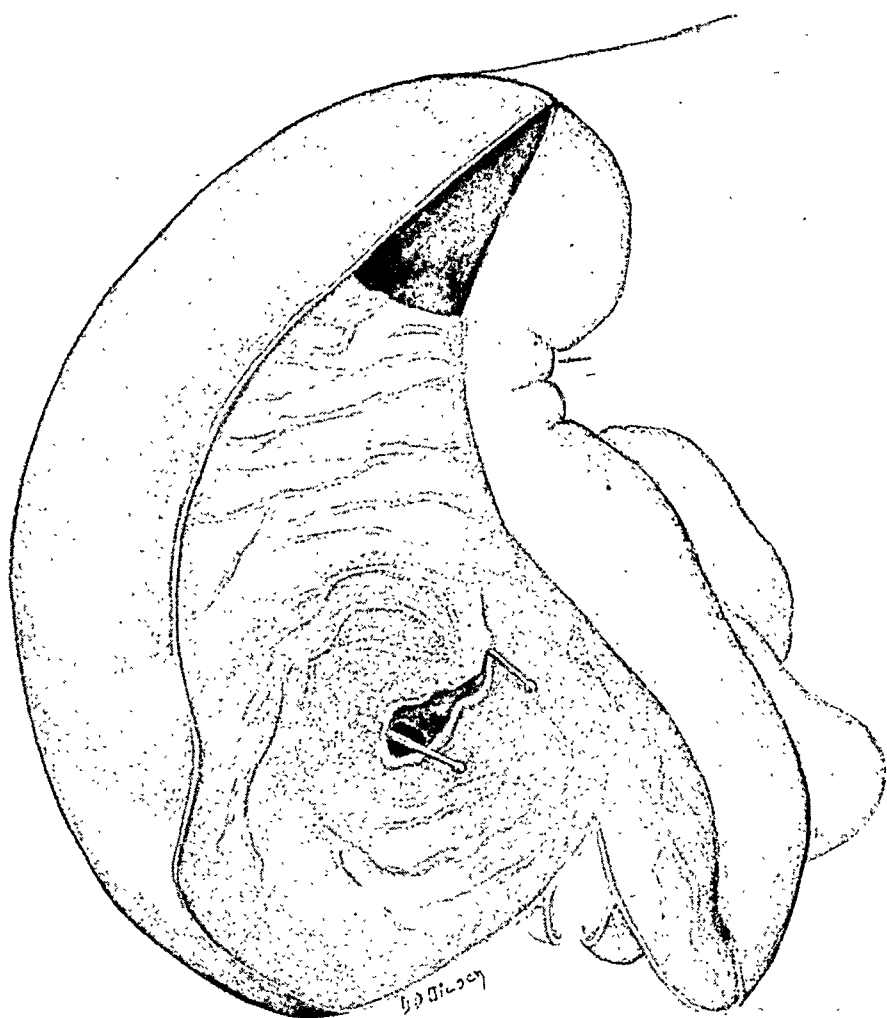


Fig. 3.—View of the concave (oral) surface of the iris-like septum narrowing the lumen of the duodenum (schematic drawing). The duodenum is opened along its convex margin, permitting a view of the oral, concave surface of the membranous septum. The opening in the septum has the shape of a reversed comma, with the head to the right and the tail to the left. The probes inserted mark the entrance of the ductus choledochus (head of the comma) and the ductus pancreaticus (tail of the comma), respectively.

pyloric ring measured on the convex margin and 8 cm. on the concave margin. One centimeter proximal to this diaphragm, the duodenum measured 15 cm. in circumference. This membranous diaphragm was dome-shaped with the peak

directed aborally, and measured 4 cm. in the ventrodorsal and 3 cm. in the transverse diameter. It had an eccentrically situated orifice about 4 mm. in diameter. On the oral, concave surface, the opening had the shape of a reversed comma, 25 mm. long, with the head to the right and the tail to the left (fig. 3). On the aboral, convex surface, the opening corresponded to the head of the comma and was situated at the dorsal end of the ventrodorsal diameter (fig. 4). The common bile duct opened in the free margin of this diaphragm. The pancreatic duct entered at the medial or tail end of the comma on the oral surface of the diaphragm.

On the external surface of the duodenum corresponding to the attachment of this membranous diaphragm there was a slight groove. A distinct narrowing of the bowel was noted at the point where the root of the mesentery crosses the inferior horizontal portion of the duodenum. Here the bowel measured 3.5 cm. in circumference, whereas, 1 cm. proximal to this point, the circumference was

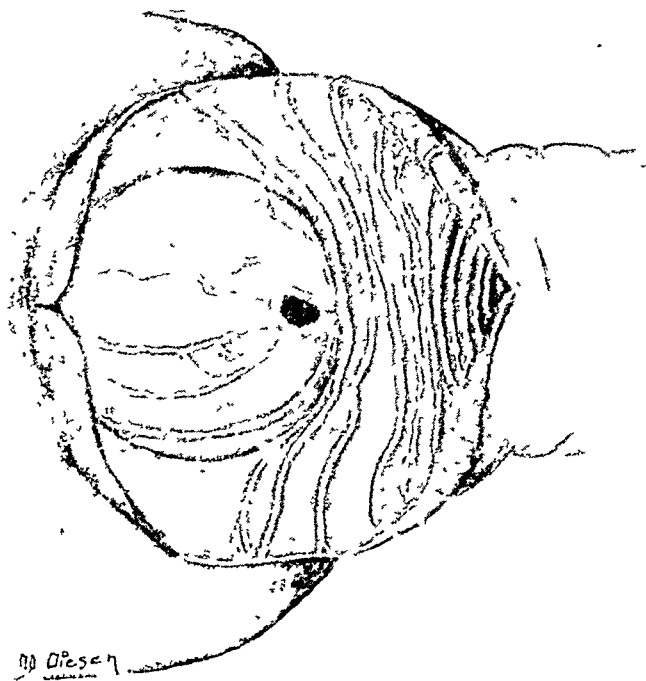


Fig. 4.—View of the convex (aboral) surface of the iris-like septum narrowing the lumen of the duodenum (schematic drawing). The duodenum is opened from the point of attachment to the membranous septum, along the free margin, permitting a view of the aboral, convex surface of the septum. The opening in this septum is eccentrically situated, measures about 4 mm. in diameter and corresponds to the head of the comma on the concave surface.

6 cm. In the portion of the duodenum aboral but adjacent to the membranous diaphragm, the folds of the mucosa were low and few in number. It appeared as if the dome of this diaphragm had pressed on the adjacent portion of the bowel wall "ironing out" the folds. The peak of the dome ended at the point where the root of the mesentery crosses the inferior horizontal portion of the duodenum.

#### COMMENT

The type of malformation of the duodenum in which the lumen of the intestine is narrowed or completely occluded at about the level of the

papilla of Vater is extremely rare. An analysis of the clinical course and observations at necropsy of the cases, records of which were available to us, reveal that these readily fall into three groups:

In the first, the membranous obstruction of the duodenum is complete, and death occurs soon after birth. The cases presented by Champneys and Power,<sup>1</sup> Wyss,<sup>2</sup> Roe and Shaw<sup>3</sup> (reported also by Keith<sup>4</sup> and Spriggs<sup>5</sup>) and by Weber<sup>6</sup> may be cited as examples.

1. Champneys and Power (1897) found at necropsy of a child, 5 days old, "that the lumen of the intestine was completely interrupted by a septum stretching across it at a point immediately upon the gastric side of the middle of the second part of the duodenum." The common bile duct entered the intestine just beyond the septum.

2. Wyss (1900) described a specimen in the pathologic anatomic collection of the Children's Hospital in Zürich, obtained in 1884, from a male infant 1½ days old. The lumen of the duodenum was divided by a membranous septum situated just above the level of the opening of the common bile duct. There was no opening in the membrane, which was 0.4 mm. thick in the center and about 0.5 mm. thick at the periphery. The circumference of the duodenum at the level of the membrane was 3 cm.; 5 cm. aborally, the circumference was 2 cm.

3. In a male infant who died suddenly on the fifth day after birth, Roe and Shaw (1911) found at necropsy a septum completely occluding the lumen of the duodenum immediately above the entrance of the common bile duct.

4. In Weber's case (1910), the female infant died on the tenth day after birth. At necropsy, a membrane was discovered, stretching across the lumen of the duodenum below the level of the papilla of Vater, completely occluding the lumen of the intestine.

5. Another most peculiar case of this type was described by Keith (1910). The specimen (in the museum of St. Bartholomew's Hospital, presented by M. T. Harrison) is "from an infant aged 9 months, who had been subject during life to recurring attacks of vomiting. The vomitus was abundant, the attacks occurring at intervals of some days.

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1. Champneys, F. H., and Power, D'Arcy: Occlusion of the Duodenum by a Complete Transverse Septum, *Brit. M. J.* **1**:718, 1897.

2. Wyss, M. O.: Ueber kongenitale Duodenal-Atresien, *Beitr. z. klin. Chir.* **26**:631, 1900.

3. Roe, W. F., and Shaw, E. H.: A Case of Congenital Atresia of the Duodenum, *Lancet* **2**:947, 1911.

4. Keith, A.: Constrictions and Occlusions of the Alimentary Tract of Congenital or Obscure Origin, *Brit. M. J.* **1**:301, 1910.

5. Spriggs, N. J.: Congenital Intestinal Occlusion, *Guy's Hosp. Rep.* **66**:143, 1912.

6. Weber, W.: Zur Kasuistik der angeborenen Atresie des Duodenums, *Med. Klin.* **6**:1294 and 1334, 1910.

There had never been a normal evacuation of the bowels, the motions being constituted by small spherical masses of faeces." A diaphragm with no evidence of an orifice "though the history of the case proves that some opening must have existed" occluded the lumen of the duodenum at about the level of the papilla of Vater. The fact that there was no record of bile having been vomited and that the bowel below the septum had a fair sized lumen supports the idea that the bile duct discharged its content below the septum, although an opening could not actually be detected in the specimen.

In the second group of these cases, the membranous obstruction of the duodenum is incomplete in that a small opening permits the passage of liquids. Trouble usually starts with the change to more solid foods. As far as we could determine, only two cases of this kind have been reported: one by Buchanan,<sup>7</sup> the other by Seidlin.<sup>8</sup>

1. Buchanan presented to the Pathological Society of London in 1861 the case of a female child, 18 months of age, who was apparently in good health until about five weeks before death; then she started vomiting and rejected everything she ate. Although vomiting had ceased two weeks before death, the postmortem appearances of the organs led to the conclusion that death was due to starvation. The necropsy disclosed "a septum stretched transversely across the calibre of the bowel" with a hole, 2.5 mm. in diameter, in the center. The septum measured about 20 mm. from the attached border to the rim of the opening. "Held up to the light," the septum showed two darker streaks traversing it from the periphery to the center: the ductus choledochus, which entered the intestine at the hole below the septum, and the pancreatic duct, which opened at the upper surface of the septum. The history being incomplete, Buchanan stated that "it is likely that while the child was at the breast, the scanty residuum of its food found no difficulty in passing the orifice of the duodenal septum, and any inconvenience was probably postponed during the time that the child, after weaning, was fed on a milk diet. Vomiting may be believed to have begun when more solid food—perhaps of an indigestible kind—was presented to the stomach, and conversely, a return to spoon food, when the child was considered an invalid, may have been the reason of the cessation of the vomiting."

2. Seidlin's case (1925) concerned a colored girl, 2½ years old, who was breast fed until 14 months of age. From the fourteenth to the eighteenth month the child continued nursing, with the addition of whole cow's milk, cereals and orange juice. From then on, the diet consisted of milk, cereals, vegetables, fruits and meats. She had always been sub-

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7. Buchanan, George: Malformation of the Duodenum in a Child, *Tr. Path. Soc. London* 12:121, 1861.

8. Seidlin, S. M.: Congenital Duodenal Septum with Obstruction, *Bull Johns Hopkins Hosp.* 37:328, 1925.

ject to constipation, but seemed to develop normally. Her trouble began three days before admission to the hospital. The only unusual item in her diet had been some canned corn, which she had eaten about two weeks before. Her mother noted that the child's abdomen had increased in size and seemed "knotted up." The following day, the child vomited several times and continued to vomit everything that was given to her, complained of abdominal pain and, for three days, retained no food. Some kernels of corn were discovered in the vomitus. During the first five days in the hospital, she was kept on a diet of milk and soft foods; she gained weight and seemed in no discomfort. She was then given a regular diet. That evening the abdomen became distended, and large peristaltic waves were noted in the upper part of the abdomen. She was again put on a diet of soft food, but the next day her appetite was poor and she vomited once. Milk was then given as the only food, but she continued to be weak and listless, developed a subnormal temperature and died on the eighth day after admission.

At necropsy, the duodenum was found to be occluded by an iris-like septum stretched across the lumen about 10 cm. above the duodeno-jejunal junction, measured along the concave margin of the duodenum. The portion of the duodenum above the septum was larger than the portion below, and its wall was considerably thickened. The septum was dome-shaped, with the convexity directed aborally. "In its most convex portion there was an eccentrically placed opening, about 7 mm. in diameter, situated somewhat posteriorly and cephalad to the center of the septum." The lumen of the opening was completely plugged with semisolid, stringy food material. On the oral side of this plug there were several kernels of corn and one bean. The common bile duct opened into the lumen of the duodenum on the aboral surface of the septum close to the margin of the septal opening after a course in the wall of the septum. The pancreatic duct passed also into the septum and opened on the oral surface of the latter at a point midway between the posterior margin of the septum and its central orifice.

In the third group of these cases, the membranous obstruction is so incomplete that from it little or no distress results during life, and the condition is usually discovered at necropsy as an incidental feature. Examples are those described by Silcock,<sup>9</sup> Keith,<sup>4</sup> and Nagel.<sup>10</sup>

1. In the case reported by Silcock (1885), the patient, a woman, aged 34, died of a generalized peritonitis secondary to a perforated intestinal ulcer. During the necropsy, a "congenital septum" was discov-

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9. Silcock, A. Q.: Epithelioma of Ascending Colon; Enterocolitis; Congenital Duodenal Septum, with Internal Diverticulum, *Tr. Path. Soc. London* **36**:207, 1885.

10. Nagel, G. W.: Unusual Conditions in the Duodenum and Their Significance, *Arch. Surg.* **11**:529 (Oct.) 1925.

ered in the duodenum "six inches below the pylorus" with a lumen barely admitting "the tip of the little finger," which apparently had caused no symptoms during life.

2. Keith (1910) described a specimen found in the collection of St. Mary's Hospital Medical School, as follows: "The dilated duodenum of an adult is crossed by a diaphragm above the opening of the common bile duct. In the diaphragm, which is ballooned downwards into the second stage of the duodenum, there is an oval orifice measuring about 5 by 3 mm."

3. Nagel (1925) reported the case of a man, aged 72, who died of pulmonary embolism after a laparotomy. At necropsy, the lumen of the duodenum was partially occluded by a transverse septum, located 1.5 cm. above the papilla of Vater. This septum was slightly concave above, was 5 mm. thick at its attachment and tapered down toward the center, where eccentrically placed, was an oval opening 8 mm. in its greatest diameter. The symptoms during life were attributed to a pseudo-diaphragmatic hernia about the hiatus oesophageus, discovered at operation. This, however, as Nagel remarked, could scarcely have been "a factor in the cause; it was probably a result of hyperperistalsis with dilatation of the oesophagus and stretching of its diaphragmatic hiatus."

In this group belong, perhaps, those cases in which one of the folds normally present in the pars descendens of the duodenum attains an unusual height, thereby narrowing the lumen of the bowel considerably. One of us<sup>11</sup> has called attention to the fact that frequently no circular plicae of any prominence are seen in the middle third of the pars descendens duodeni, the fold immediately above the plica longitudinalis and the first fold below the opening of the papilla being more prominent than any of the others (fig. 5).

Our case appears to belong rather to the second than to the third group. The duodenum was partially obstructed, permitting the passage of certain solid foods, but as the result of mechanical plugging, it was probably completely occluded at times. This condition was aggravated because increased intraduodenal pressure caused the septum to bulge toward the area where the crossing of the mesentery could offer an added hindrance to the free passage of the duodenal contents.

The rupture of the stomach is also of unusual interest. There is no doubt that most of the fluid used in the enemas traversed the intestine and entered the stomach with a resulting overdistention of the latter. Dragstedt<sup>12</sup> demonstrated that fluid introduced into the rectum of a dog, under a hydrostatic pressure of 150 cm., will traverse the entire bowel

11. Halpert, Béla: The Arrangement of Folds in the Pars Descendens Duodeni, with Special Reference to Their Relationship to the Papilla of Vater, *Anat. Rec.* 32:232, 1926.

12. Dragstedt, C. A.: Personal communication.



and cause great overdistention of the stomach and death of the animal within from eighteen to twenty-four hours. In our patient, the hypertrophied wall of the stomach may have caused more powerful contractions; these and the other forces concerned in the act of vomiting probably induced the rupture near the site of transition of the esophagus to the stomach.

A survey of the available literature of the past ten years reveals only three instances of rupture of the apparently normal stomach from overdistention, and none associated with stenosis of the duodenum.

Busch<sup>13</sup> summarized the literature on this subject to 1924 and reported one case, in which the rupture occurred following great overdistention from the excessive intake of food. From this and the previously reported cases, Busch concluded that rupture of the normal

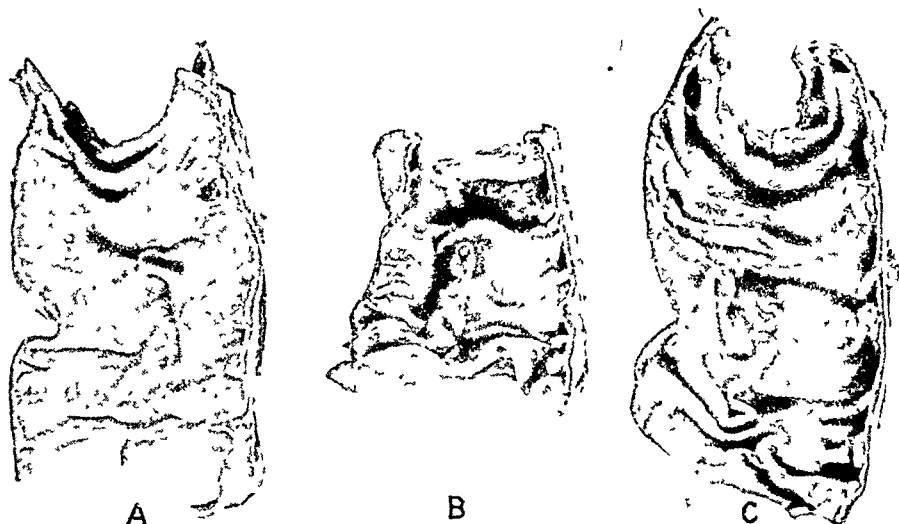


Fig. 5—Photographs of the region of the papilla of Vater showing that the middle third of the pars descendens duodeni is void of circular plicae of any prominence, the fold above and the first circular fold below the opening of the papilla being more prominent than any of the others. A noteworthy feature in all three of these is the presence of a plica longitudinalis infrapapillaris which has nothing to do with the plica longitudinalis suprapapillaris (present only in fig. 5 A), a fold indicating the course of the intramural portion of the ductus choledochus.

stomach is an extremely rare condition and arises only in the course of an acute dilatation of the stomach. The usual place of rupture in the cases reported was in the lesser curvature near the cardia.

More recently, Murdfield<sup>14</sup> reported the case of a man, aged 39, who attended a feast and drank unusual quantities of beer. Because of later

13. Busch, Max: Ein Beitrag zur Frage der vollständigen Magenberstung, *Frankfurt. Ztschr. f. Path.* **30**:30, 1924.

14. Murdfield, P.: Akute Magenruptur nach Einnahme von Natrium Bicarbonicum, *Klin. Wchnschr.* **5**:1613, 1926.

distress, he took a "Messerspitze" of sodium bicarbonate. Severe pains soon appeared in the upper part of the abdomen, and at laparotomy the following day a tear, 5.3 cm. long, was found in the "Magenstrasse," 4.7 cm. from the cardia. The mucosa around the tear appeared normal, and there was no evidence of a perforating ulcer. The abdominal cavity contained from 6 to 8 liters of fluid and food. Murdfield believed that the huge quantities of beer and food led to overdistention and acute dilatation of the stomach; the addition of sodium bicarbonate caused the rapid formation of carbon dioxide, with the rupture occurring soon thereafter. In confirmation of this view, Murdfield stated that the introduction of 3 liters of from 0.3 to 0.4 per cent hydrochloric acid plus a "Messerspitze" of sodium bicarbonate into the stomachs of fresh cadavers led to the rapid formation of gas and frequently to rupture, always in the lesser curvature and nearer to the cardia than to the pylorus.

The third case, reported by Mariantschik,<sup>15</sup> was that of a man, aged 33, who ate salt herring and drank much water during the night. On the following morning, he drank a cup and a half of cocoa and went to work. Shortly afterward he jumped from his wagon, a distance of about two and one-half feet. One and one-half hours later he had sharp abdominal pains, which increased in severity. Laparotomy some hours later disclosed a perforation of the stomach near the pylorus. The wall around the site of rupture appeared normal, and no ulcer could be found.

#### SUMMARY

This paper presents the clinical history and observations at necropsy of a girl, aged 8, with chronic intermittent high intestinal obstruction, acute occlusion of the duodenum and rupture of the stomach. At about the level of the papilla of Vater, a membranous septum with a small iris-like aperture narrowed the lumen of the bowel. The dome of the bulging septum extended to the point at which the mesentery crossed the inferior horizontal portion of the duodenum. The marked hypertrophy of the wall of the duodenum oral to the septum, and that of the stomach, as well, indicated that the site of chronic obstruction was at this point. The acute occlusion was apparently caused by a plugging of the aperture in the septum by coarse food, aided by the mechanical hindrance offered by the crossing of the mesentery. The overadministration of enemas in an attempt to relieve the symptoms of an acute obstruction led, by overdistention and increased motor activity, to rupture of the stomach.

The reports of similar cases are reviewed.

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15. Mariantschik, L. P.: Ein Fall intraabdominaler Magenruptur traumatischen Ursprungs mit nachfolgender Perforation, *Zentralbl. f. Chir.* 53:1050, 1926

# REPEATED EXPOSURE TO HIGH TEMPERATURE

## EFFECT ON LYMPHOID TISSUE AND ON LEUKOCYTE COUNT \*

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AND

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It has been shown by Murphy and Sturm<sup>1</sup> that a single heating of mice for five minutes at a temperature of 60 C. is followed by a prompt fall in the total white cell count, both polymorphonuclear leukocytes and lymphocytes being affected. This initial fall was succeeded by a slow recovery of the polymorphonuclears and a rapid rise of lymphocytes which reached its peak at about the end of the second week and then gradually fell to the normal level. During the period of the most marked increase in the number of white cells, many lymphocytes were observed undergoing mitosis in the blood stream. Nakahara<sup>2</sup> studied the gross and microscopic pathologic changes in the group of mice mentioned and observed a marked enlargement of the lymph glands and spleen which reached its maximum on from the sixth to the eighth day, and by the fourteenth day had returned to normal. Immediately following the heating there were widespread degeneration and necrosis, followed in forty-eight hours by marked proliferation of cells of the germinal centers with many mitotic figures. On the fourteenth day, these organs again appeared to be normal. Nakahara concluded that the lymphocytosis thus induced was due, in part at least, to the enhanced proliferative activity of the germinal centers in the spleen and lymph glands which reacted to the destructive effect of heat on the lymphoid cells.

In view of the aforementioned observations, it seemed to be worth while to study the effects of repeatedly submitting mice to a high temperature on the lymphocytes of the blood, lymph glands and spleen. Each heating, after the first, was done at a time when the white cell count was at about its peak following the previous heating.

### APPARATUS

The apparatus used consisted of a heating chamber made from a 10 inch (25.4 cm.) cylinder of asbestos, enclosing a 100 watt frosted electric light bulb in the lower portion of the cylinder and a small net wire cage above in which the

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\* Submitted for publication, May 21, 1929.

\* From the Department of Pathology of Northwestern University Medical School.

1. Murphy, J. B., and Sturm, E.: *J. Exper. Med.* **29**:1, 1919.

2. Nakahara, W.: *J. Exper. Med.* **29**:17, 1919.

mice were placed. A thermometer was suspended between the top of the bulb and the cage. By the use of compressed air it was possible to maintain proper ventilation and a constant temperature, thus lowering the mortality rate during the heating. In the various groups heated in this manner a temperature of from 60 to 65 C. was maintained over a period of five minutes.

# EXPERIMENTS

*Group 2A.*—Group 2A consisted of ten mice, the average normal white cell count of which was: 4,300 polymorphonuclear leukocytes and 7,600 lymphocytes. These mice were heated for five minutes at a temperature of 60 C. at ten day intervals, blood counts being made on only two or three mice before and after each heating, since it has been shown that too frequent counts on the same animal cause a wide fluctua-

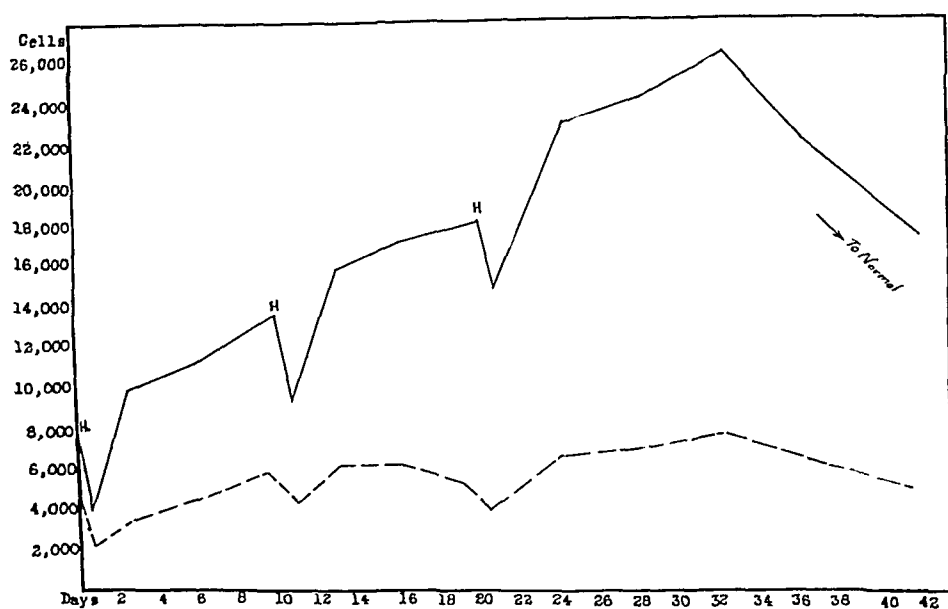


Fig. 1.—Composite leukocyte curve for group 2A (ten mice) heated three times. The solid line represents the lymphocytes; the broken line, the polymorphonuclear leukocytes, and H, the points of heating.

tion. Although this group was heated only three times, it is recorded principally to show the enormous rise in the number of lymphocytes that can be produced by repeated subjections to high temperature (fig. 1).

The initial fall in both polymorphonuclear leukocytes and lymphocytes immediately following exposure to heat was noted, with a slow rise of the former and a rapid rise of the latter. On the tenth day after the first heating and with the lymphocytes showing an increase of 6,000 cells above normal, the mice were heated a second time, again resulting in the initial fall followed by a rise in lymphocytes, but little or no change in the polymorphonuclear cells. On the twelfth day following

the third heating, the white cell count reached its peak. The count at this time was: 7,800 polymorphonuclear leukocytes and 26,600 lymphocytes, making a total white cell count of 34,400 cells per cubic millimeter. Subsequent counts showed a gradual fall to normal.

*Groups 1B and 2B.*—For the purpose of recording both tissue sections and blood picture, these two groups have been combined. The two groups consisted of seven mice each, the average normal white cell count being 3,900 polymorphonuclear leukocytes and 8,000 lymphocytes. The heating procedures were carried out in a manner similar to that described; these groups, however, received fourteen heatings and were observed over a period of 210 days (fig. 2).

During the first forty days, the observations on the blood picture of this group were essentially similar to those of the previous group

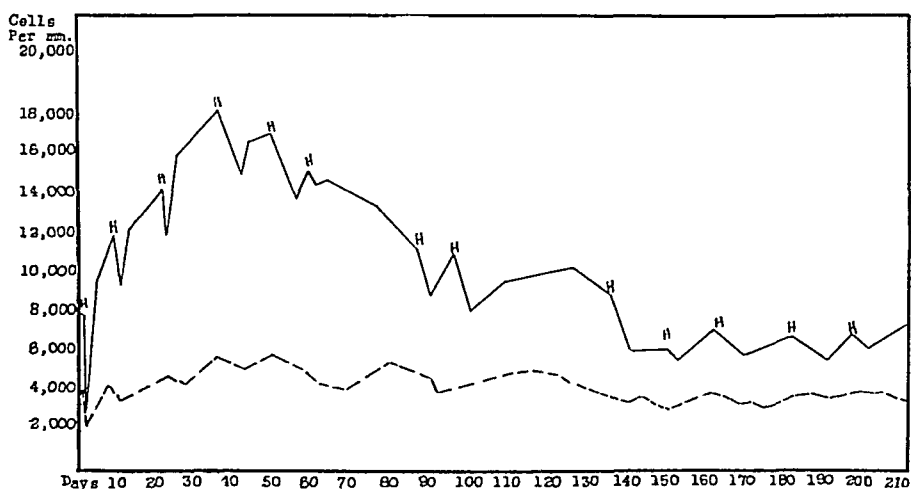


Fig. 2.—Composite leukocyte curve for groups 1B and 2B (fourteen mice) heated thirteen times. The solid line represents the lymphocytes; the broken line, the polymorphonuclear leukocytes, and H, the heatings.

recorded, there being always the initial fall in the number of both polymorphonuclear leukocytes and lymphocytes followed by a slow recovery of the former and a more rapid rise of the latter after each heating. During the initial period, there was a stairstep rise in the number of white cells, primarily lymphocytes, up to 25,000 cells per cubic millimeter. From this point, however, the number of white cells, principally lymphocytes, began to fall gradually, and little fluctuation was noted following subsequent heatings. During the last thirty days of observation, the white cells were found to be at or below the normal count.

Sections of the spleen made immediately following the heating procedure, at a time at which the circulating white cells were at their lowest level, showed a marked necrosis, principally of the cells of the germinal

centers; sections made forty-eight hours later from a spleen that was grossly four times the normal size and at a time at which the circulating white cells were gradually rising, the germinal centers were much larger than normal and showed definite evidences of proliferation, the most important of which was the presence of many cells undergoing division. Our results, therefore, confirm those of Nakahara.<sup>2</sup>

Sections made ninety days after the initial heating showed a generalized increase in fibrous tissue in the spleen. The progressive increase in fibrous tissue was largely at the expense of the germinal centers and splenic corpuscles. After 210 days, when the circulating white cells



Fig. 3.—Fibrosis of the spleen after thirteen heatings or 210 days after the first heating;  $\times 10$ .

were below the normal level, the spleen showed a marked diffuse fibrosis, patchy in distribution, with irregular areas of dense fibrous tissue that had replaced much of the normal splenic tissue. These areas made up 50 per cent or more of the spleen at this stage. Between these patches of fibrosis were areas of varying lymphoid content, irregular in outline, but generally of small dimensions (fig. 3).

Recently, we have subjected a small series of splenectomized mice to a similar heating procedure after complete recovery from the operation. In this group of animals the initial fall following heating was similar to that of the previous groups, but the rise in the number of lymphocytes was much slower and the maximum increase much smaller.

## COMMENT

Repeatedly subjecting mice to dry heat at 60 C. at intervals of ten days results in the following changes in the leukocytes of the circulating blood:

(a) Soon after the heating there is a marked leukopenia followed by a marked rise in the number of white cells, which reaches the maximum number from ten to fourteen days later. The chief change in each instance was in the lymphocytes.

(b) In these experiments, this increase reached its peak about ten days after the third, and forty days after the initial, heating. At this time, in one series of animals the total white cell count reached a maximum of 34,400, of which 77 per cent were lymphocytes.

(c) After the fourth heating, each subjection to high temperature produced successively less and less effect and the number of white blood cells in the circulating blood gradually diminished. In one series of mice the total white cell count on the fortieth day was 23,700, of which 76 per cent were lymphocytes. In this same series, on the 200th day and after thirteen heatings the total number of white cells was approximately 10,000, of which 60 per cent were lymphocytes. The normal leukocyte counts of these mice was slightly more than 11,000, with an average of 65 per cent of lymphocytes. The lymphocyte counts of normal mice as reported in the literature have varied between a total of 5,000, with 62 per cent lymphocytes (Young<sup>3</sup>); 8,000 to 10,000 with 71 per cent lymphocytes (Goodall<sup>4</sup>), and 6,000 to 11,000 with from 50 to 60 per cent lymphocytes (Simonds<sup>5</sup>) per cubic millimeter. Murphy and Sturm<sup>1</sup> have recorded the highest allegedly normal leukocyte counts in mice of from 10,800 to 24,000, with from 54 to 65 per cent lymphocytes. The averages in our series, therefore, compare with the high normals of other observers, except those of Murphy and Sturm. The percentage of lymphocytes at the peak of the leukocytosis following heating of these mice exceeds considerably the maximum percentage recorded by any other observer. Hence, repeatedly heating mice at intervals of ten days results in a lymphocytosis which increases up to about the fortieth day, or the third or fourth heating, and then gradually subsides. The percentage of lymphocytes after 200 days, or twelve or thirteen heatings, is approximately normal. The maximum increase was 225 per cent above the original lymphocyte count for the series.

(d) During the period of heating the mice, the fluctuations in the number of polymorphonuclears were less marked than those in the

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3. Young, J.: *Edinburgh M. J.* **28**:233, 1922.

4. Goodall: *J. Path. & Bact.* **14**:195, 1909.

5. Simonds: *Anat. Rec.* **30**:99, 1925.

number of lymphocytes. The peak was reached about ten days later than in the case of the lymphocytes. The maximum increase was about 70 per cent above the original normal.

The changes in the spleen and lymph glands following repeated heatings of the mice were:

(a) Localized areas of necrosis in the lymph glands and spleen in the first twenty-four hours, followed by a marked hyperplasia of the lymphoid elements, as pointed out by Nakahara. The alternating changes continue until about the fortieth day, or the third or fourth heating.

(b) After this time fibrosis begins and increases with each successive heating until after 200 days or from twelve to thirteen heatings, the spleen, although still much larger than normal, shows an extreme grade of fibrosis. At this time no lymph glands could be found on gross examination. On microscopic examination, sections of fat and connective tissue from the inguinal region failed to reveal lymphoid tissue.

The changes in the leukocyte count can apparently be correlated with the alterations in the spleen and lymph glands. Repeated heatings at intervals of ten days result in a marked lymphocytosis until fibrosis of the spleen and lymph glands begins. With increasing fibrosis, heating produces less and less effect on the blood picture until after about 200 days, or from twelve to thirteen heatings, the effect is negligible.

#### SUMMARY

Repeatedly heating mice at 60 C. for five minutes at intervals of ten days results in (a) a temporary lymphopenia, followed by (b) an increasing lymphocytosis up to about the fortieth day or the third or fourth heating. After this time each successive heating becomes less and less effective until, after about 200 days or twelve or thirteen heatings, the total leukocyte count and the percentage of lymphocytes return to or below normal and show little or no effect from further heating.

The diminishing effect of successive heatings on the leukocyte count after about the fortieth day is accompanied by an increasing fibrosis of the spleen and lymph glands.



# IRON-INCRUSTED FIBER INCLUSIONS OF GIANT CELLS \*

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Necrotic tissues and a variety of products resulting from degeneration of tissue act within the living host as foreign substances and stimulate the production of chronic granulation tissue, which commonly is designated a "foreign-body" tissue reaction.<sup>1</sup> Giant cells of the "foreign-body" variety are important constituents of these lesions, and they enclose or are closely approximated to the masses of the irritant substance. The certain identification by staining methods of some of the necrotic tissue substances or of their derivatives provoking the lesions is hindered at times or even thwarted because of the changes in their chemical composition or staining qualities accompanying degeneration, and because of incrustation with inorganic substances such as the salts of iron and calcium. Among the tissue substances commonly acting as foreign bodies are derivatives of the stroma, particularly elastic tissue fibers. Elastic fiber inclusions seem to have been observed in giant cells many years ago. Rona's<sup>2</sup> report of 1900 stated that Ssudakewitsch in 1889 first accurately described elastic fiber inclusions of giant cells, but before this, Virchow, Billroth, Schuppel and Lang had seen them. The giant cells with elastic fiber inclusions seen by Rona were in tuberculous and leprous lesions of the skin. He discovered that these fibers were incrustated with iron, and concluded that a degeneration of the elastic fibers within the giant cells favored the selective adsorption of iron diffused in the tissues. Hektoen,<sup>3</sup> in 1902, reported to the Chicago Pathological Society elastic fiber inclusions of giant cells in a healed hemorrhoid nodule and in tissues of an enlarged and bulbous nose. The fibers in the hemorrhoid nodule, only, contained iron.

Elastic fibers incrustated with calcium and iron causing inflammatory reactions have been observed a number of times in lung tissues.

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\* Submitted for publication, May 20, 1929.

\* From the Henry Baird Favill Laboratory, St. Luke's Hospital.

\* Aided by the Winfield Peck Memorial Fund.

1. Haythorn, S. R.: Multinucleated Giant Cells, Arch. Path. **7**:651 (April) 1929.

2. Rona, P.: Ueber das Verhalten der elastischen Fasern in Riesenzellen, Beitr. z. path. Anat. u. z. allg. Path. **27**:349, 1900.

3. Hektoen, L.: The Absorption and Incrustation of Elastic Fibers in Giant Cells, Tr. Chicago Path. Soc. **5**:51, 1902.

Bittroff<sup>4</sup> saw them in the lungs of a woman 25 years of age who had a marked chronic passive hyperemia due to cardiac decompensation. Many giant cells with elastic fiber inclusions were seen in the histologic preparations of the lungs. The inclusions reacted specifically with the microchemical tests for iron and calcium, and to some extent with the stains for elastic fibers. Bittroff concluded that the fibers were degenerated elastic tissue impregnated with iron and calcium. A similar report, he stated, had been made by Kockel. Schum,<sup>5</sup> in 1912, reported similar changes in the lungs of a man 47 years of age who for many years had had chronic asthma. He referred to other reports by Davidsohn and Krückmann. Gignon,<sup>6</sup> the next year, published another account of iron and calcium incrustations of tissue fibers in the lungs with chronic passive hyperemia. These tissue derivatives were found both intracellularly and extracellularly. Kraus<sup>7</sup> somewhat later reported the results of a comprehensive study of siderotic lesions of the spleen from a woman 47 years of age who had lymphatic leukemia. Some of the pigment deposits, he believed, were hemosiderin, some, hematoïdin or a precursor, and others, greenish-yellow and arranged in coarse and fine bands, sometimes in wisps and sprays, he considered to be, at least in part, iron phosphate. He found the last-mentioned deposits chiefly in hyalinized fibrous tissue, but could not establish their absence in the connective tissue fibers themselves. Kraus previously had seen similar pigmentations in old infarcts of three spleens, and after the completion of his extensive study, saw them in another old infarct scar of the spleen and also in a markedly atrophic spleen. Aschoff, in 1905, reported the presence of iron crystals in a leukemic spleen, and, in a personal communication to Kraus, expressed the belief that they were identical with those which he (Kraus) had studied. Iron incrustations of connective tissue fibrils with hemochromatosis and focal hemorrhages were reported by Schuppisser.<sup>8</sup> In the spleen, he found the collagenous and the elastic fibers incrustated with iron, and he referred to a statement by Ehrlich that elastic fibers of living tissues in the vicinity of hemorrhages had the peculiar property of becoming impregnated with compounds of iron. Schuppisser believed that the compounds in his

4. Bittroff, R.: Ueber kalk und eisenhaltige elastische Fasern in der Lunge, Beitr. z. path. Anat. u. z. allg. Path. **49**:213, 1910.

5. Schum, H.: Bildung von Fremdkörper Riesenzellen um degenerierte elastische Fasern, Virchows Arch. f. path. Anat. **208**:446, 1912.

6. Gignon, A.: Eisen und Alkaliemprägung des Lungengewebes, Beitr. z. path. Anat. u. z. allg. Path. **55**:46, 1913.

7. Kraus, E. J.: Ueber ein bisher unbekanntes eisenhaltiges Pigment in der menschlichen Milz, Beitr. z. path. Anat. u. z. allg. Path. **70**:234, 1922.

8. Schuppisser, H.: Ueber Eiseninkrustation der Bindegewebssubstanzen bei Hämochromatose und bei lokalen Blutungen, Virchows Arch. f. path. Anat. **239**:320, 1922.

tissues were the hydroxide and phosphate of iron. Sigmund<sup>9</sup> also reported iron deposits in the spleen like those described by Kraus. He had seen them in old infarcts of the spleen and stated that they occur in the spleen with hemolytic icterus and so-called Banti's disease. The deposits are visible macroscopically as brown spots in the trabeculae of the spleen, usually associated with changes in the walls of the blood vessels. These iron deposits, he stated, are present especially in the elastic fibers which become necrotic and break up into segments, and are surrounded by foreign body giant cells. In unstained sections, the pigment is yellow-green or some similar color; usually it is associated with hemosiderin and hematoidin, and originates from the disintegrated blood of hemorrhages. Lubarsch,<sup>10</sup> commenting on the siderotic nodules of the spleen described by others, stated that these contain connective tissue fibers infiltrated with calcium or iron, or both, in the form of curious structures, in coils, granules or other shapes. The peculiarity of this pigmentation is that much is not in cells, but is an infiltration of the stroma fibers and vessel walls. Lubarsch saw these incrustations in an ovary and in an old infarct of the spleen in which both elastic and collagenous fibers were incrustated with iron and calcium. These fibers had stimulated a foreign body tissue reaction. Lubarsch referred to a similar observation by Talmann<sup>11</sup> in an aberrant nodule of splenic tissue. Other reports of iron and calcium incrustations of the spleen have been made by Christeller and Puskeppelies,<sup>12</sup> Klinge,<sup>13</sup> Nicod,<sup>14</sup> Pick<sup>15</sup> and Hennings,<sup>16</sup> and these authors refer to Eppinger's original observation. More recently Hogenauer<sup>17</sup> added another report. Pick stated that in addition to the vascular and perivascular destruction of the elastic and collagenous tissue elements in the spleen

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9. Sigmund: Demonstration ungewöhnlicher Eisenablagerungen, *Centralbl. f. allg. Path. u. path. Anat.* **33**:207, 1922-1923.

10. Lubarsch, O.: Ueber die hämoglobinogenen Pigmentierungen, *Klin. Wchnschr.* **4**:2137, 1925. Henke-Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie* **1-2**:480, 1927.

11. Talmann, I.: Nebenmilzen im Nebenhoden und Samenstrang, *Virchows Arch. f. path. Anat.* **259**:237, 1926.

12. Christeller, E., and Puskeppelies, M.: Die periarteriellen Eisen-und Kalkinkrustationen in der Milz, *Virchows Arch. f. path. Anat.* **250**:107, 1924.

13. Klinge, F.: Ueber die Entstehung der periarteriellen Eisen-und Kalkinkrustationen in der Milz, *Virchows Arch. f. path. Anat.* **255**:599, 1925.

14. Nicod, J.: Essai d'analyse d'un pigment ferrique rare, *Schweiz. med. Wchnschr.* **8**:200, 1924; abstr. *Centralbl. f. allg. Path. u. path. Anat.* **36**:81, 1925.

15. Pick, L.: Zur Frage der Eisen-und Kalkablagerung in der Milz, *Klin. Wchnschr.* **4**:517, 1925.

16. Hennings, K.: Ein Beitrag zur periarteriellen Kalk-Eiseninkrustation der Milz, *Virchows Arch. f. path. Anat.* **259**:244, 1926.

17. Hogenauer, F.: Zur Frage der ausgedehnten Eiseninkrustation in der Milz, *Virchows Arch. f. path. Anat.* **269**:685, 1928.

and their incrustation with iron there is calcification of the incrustated structures, then a demarcation of the focus by chronic granulation tissue, a fibrous tissue encapsulation and the formation of foreign body giant cells in the granulation tissue. He gives as essential factors: (1) an increased destruction of the red blood cells following hemorrhage and leading to a maximal production of hemosiderin, and (2) a destruction of the elastic and collagenous tissues in sclerotic vessels or scars, which provide the matrix that becomes saturated with dissolved hemosiderin.

Such foreign-body reactions toward derivatives of stroma tissues, incrustated with iron compounds, have been observed at St. Luke's Hospital, Chicago, in tissues removed surgically from various places.

CASE 1.—Both fallopian tubes and the fundus of a uterus were removed surgically from a woman, aged 29, by Dr. A. H. Curtis. The tubes were 8 cm. long and from 1.7 to 2 cm. in diameter. The proximal end of each was rounded and sealed by fibrous tissue. Within the lumen of one was a small amount of red-brown fluid, and in the other, a thick yellow exudate. The linings were white and scarred in a number of places. In sections stained with hematoxylin and eosin, the lining of the fallopian tubes was thickened by masses of tuberculous chronic granulation tissue with focal round or oval structures histologically tubercles. In these were Langhans giant cells and also others, equally large, of the foreign-body variety. Within such giant cells or closely approximated to them were coarse fibril inclusions, several wrapped together like the layers of an onion. These, with a little granular substance, usually were in a clear portion of the cell. The staining qualities of the inclusions were as follows: with phosphotungstic acid-hematoxylin, yellow; Mallory's aniline blue, blue; van Gieson's connective tissue stain, lavender to red; Foot and Ménard<sup>18</sup> silver stain for reticulum fibers, dark red; Weigert's elastic tissue stain, faint lavender; Verhoeff's elastic fiber stain, variable-dark purple or green-yellow; ammonium sulphide test for iron, brown-black; potassium ferrocyanide test for iron, blue—a few red. In preparations stained for acid-fast bacilli, slightly curved, rodlike structures were found in the granulation tissue histologically tuberculous.

CASE 2.—The lymph node was contained in axillary fat removed with a mammary gland from a woman, aged 60, by Dr. S. M. Harsha because of carcinoma. The histologic preparations of the lymph node were without tumor, but they contained discrete and confluent masses of chronic tuberculous granulation tissue with the usual Langhans giant cells and also foreign-body giant cells with inclusions composed of coarse, concentrically arranged fibrils (fig. 1). The staining reactions were essentially the same as those mentioned in case 1. Granular, rodlike structures resembling tubercle bacilli were found in sections stained for acid-fast organisms.

CASE 3.—A cervical lymph node was removed for diagnosis by Dr. H. E. Jones from a negress, aged 24, with sickle cell anemia. The histologic preparations included large masses of chronic tuberculous granulation tissue with oval or round tubercles containing Langhans giant cells and foreign-body giant cells with inclusions of coarse concentrically arranged fibrils or hyaline masses like those men-

18. Foot, N. C., and Ménard, M. C.: A Rapid Method for the Silver Impregnation of Reticulum, *Arch. Path.* 4:211 (Aug.) 1927.

tioned. The staining reactions, also, were in every respect as stated. Several structures resembling acid-fast bacilli were found.

CASE 4.—The tissues were removed by Dr. E. W. Ryerson from the dorsal surface of the foot of a white woman, aged 20. The incision made in correcting a simple bone deformity failed to heal. The surgical gauze dressings were regularly stained with bright red blood. For a long time the indolent nature of the ulcer was without explanation. Cultures of the exudate in the wound and of the tissues removed failed to demonstrate bacteria other than those usually present

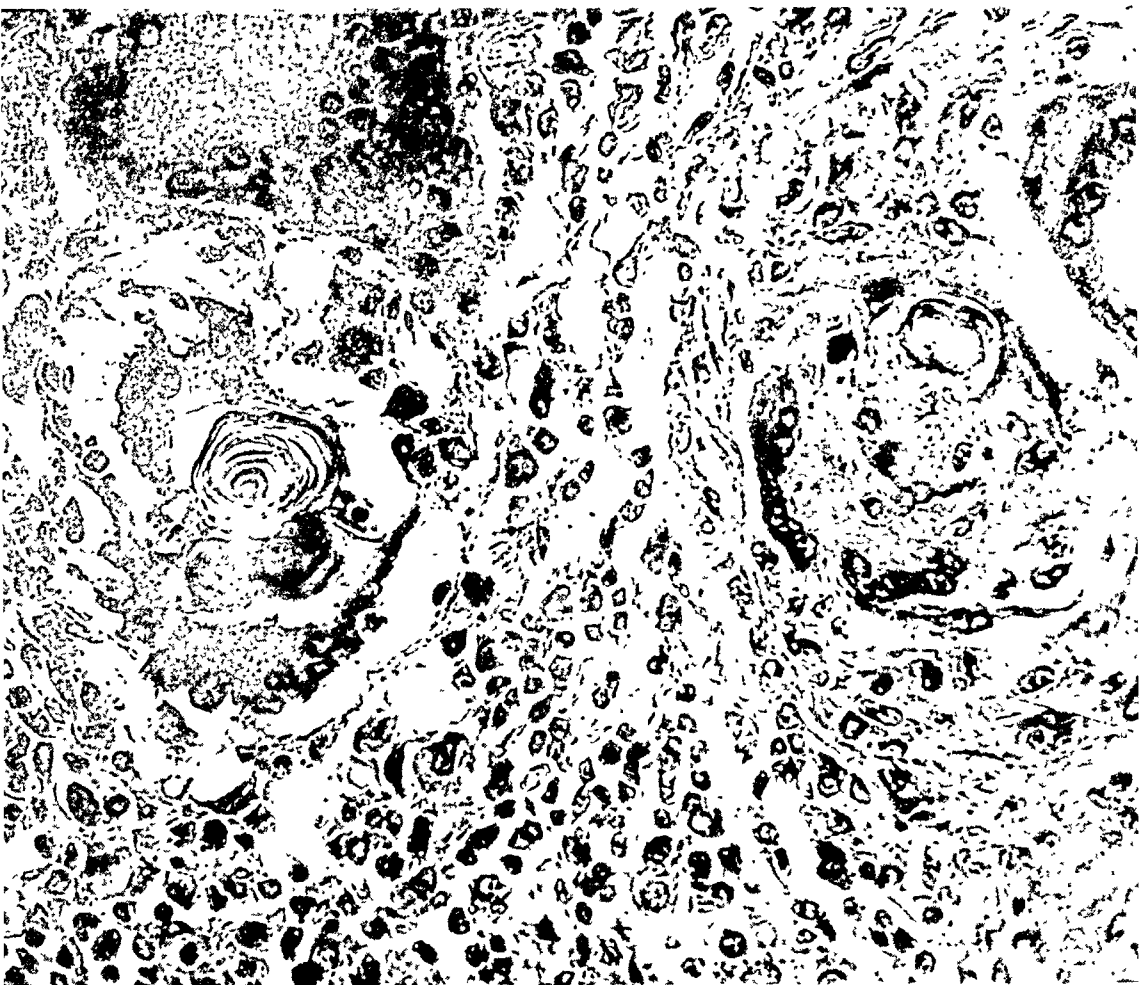


Fig. 1.—Photomicrograph to illustrate the concentrically arranged, iron-incrusted fiber inclusions in two giant cells (case 2);  $\times 515$ .

on skin surfaces or fungi which could be considered accountable for the chronic ulcer. Finally, the suspicion, entertained for some time, that this patient was malingering, was verified. In histologic preparations there was a chronic non-specific granulation and scar tissue reaction of the corium and subcutaneous tissues, and on the surface of the ulcer was an acute exudate. Some of the cellular portions of the chronic granulation tissue included coarse granular masses of yellow-brown pigmented material, some extracellular, some within large mononuclear cells and some within giant cells of the foreign-body variety. Also, there

were coarse, yellow, linear structures like the fibrils of connective tissue. Some of these, with branched ends like the fructifications of a mycelium, had both yellow and purple portions in the hematoxylin-eosin stained preparations. Besides these were similar yellow structures transversely segmented and not unlike the segmentations of coarse mycelial threads. The stains mentioned were used in examining these tissues. The yellow fibrils had none of the staining reactions of connective tissue. Certain fibrils, slightly yellow, stained faintly blue with Weigert's elastic stain, and some of these were in tangled masses of coarse threads. The yellow masses and fibrils reacted strongly with the microchemical tests for iron. In the scar tissue were disarranged coarse fibers stained like elastic tissue

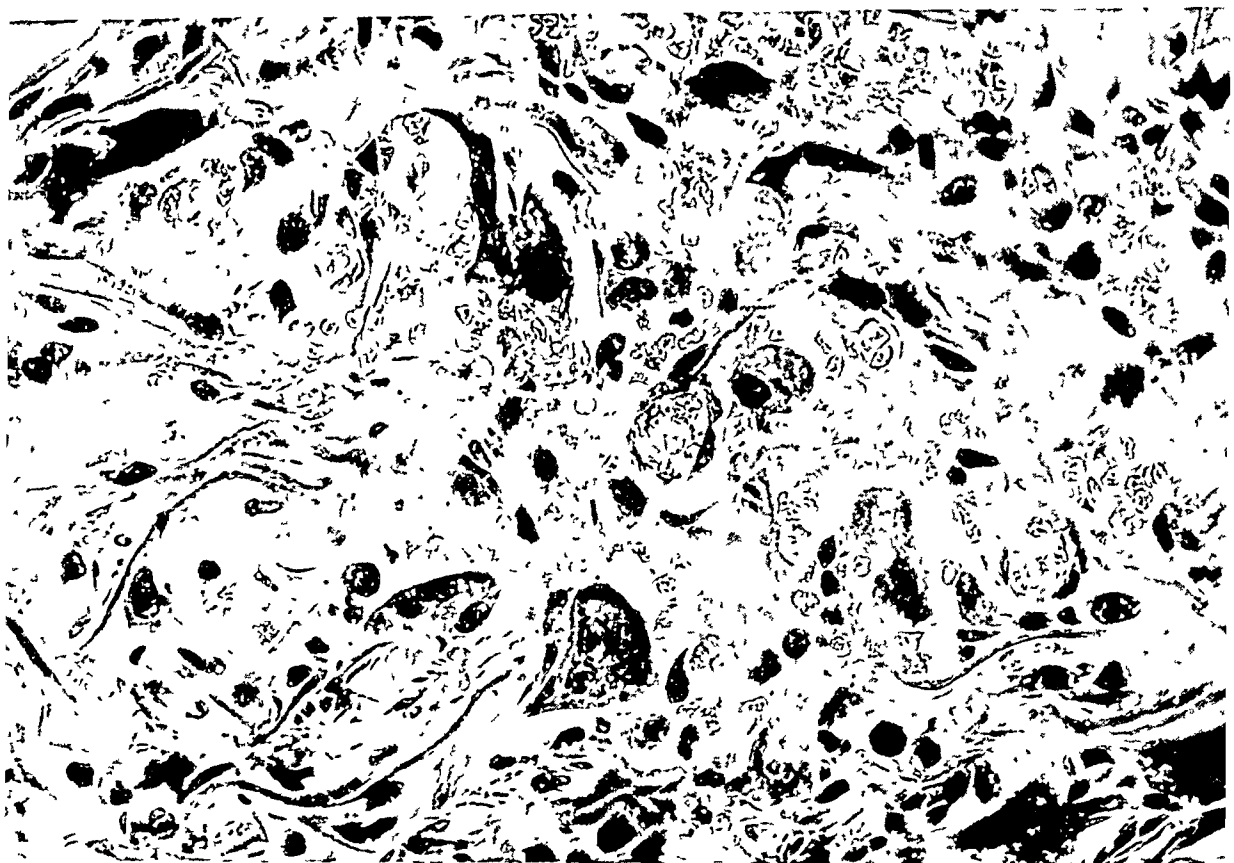


Fig. 2.—Photomicrograph of the granulation tissue with disarranged coarse fibrils and foreign-body giant cells (case 5). These fibers contained little or no iron; reduced from a magnification of  $\times 515$ .

CASE 5—A mass of chronic granulation tissue was removed, by Dr. W. F. Lyon, from a draining wound of the forehead of a white man, aged 26, five months after a laceration of the soft tissues and a depressed fracture of the frontal bone, complicated by osteomyelitis. In this chronic granulation tissue were aggregations of foreign-body giant cells in close approximation to threads and coarse fibrils with a faintly yellow cast. These varied considerably in length and in their arrangement in the tissues (fig. 2). With the phosphotungstic acid-hematoxylin stain, many of these fibrils had the color of collagenous connective tissue, considerably diminished in intensity and with an affinity for the purple component of the stain. The microchemical reaction (prussian blue) for iron was negative or faint.

## COMMENT

Connective tissue fibers with or without incrustations of iron and associated in the tissues of the host with foreign-body granulation tissue have been observed in tuberculous lesions of lymph nodes and fallopian tubes, and in nonspecific granulation tissue of the skin. The results with the stains for collagenous and elastic fibers are uncertain, and probably fibrils of both have initiated the foreign-body reactions and have become incrustated with the salts of iron.

# ANAPHYLACTIC CROSSED RELATIONSHIP BETWEEN HORSE DANDER AND HORSE SERUM \*

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It is generally assumed that there is some relationship between hypersensitiveness to horse dander and hypersensitiveness to horse serum. Positive skin reactions to both horse dander and horse serum, however, do not always appear in one person. The majority of these patients react to horse dander alone.

Longcope, O'Brien and Perlzweig,<sup>1</sup> in 1925, were the first to approach this problem from an experimental standpoint. They concluded that there was no crossed anaphylactic relationship between horse dander and horse serum. At about the same time, we were also engaged in studying this problem, and a preliminary report<sup>2</sup> was made in 1925, which appeared immediately after the publication of the experiments of Longcope and his co-workers. Contrary to their conclusions, we stated that a crossed anaphylactic relationship does exist. Our studies have been continued to the present time, and we are now prepared to present protocols in detail to substantiate our preliminary statement.

## EXPERIMENTAL WORK

All the animals were normal.<sup>3</sup> Each animal was sensitized to either horse dander or horse serum and received a crossed injection of horse serum (or diphtheria antitoxin) or of horse dander extract. All animals not killed by the crossed shock injection were given a second shock injection one hour later of the

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\* Submitted for publication, May 27, 1929.

\* From the Departments of Immunology and Pediatrics, University and Bellevue Hospital Medical College, New York University.

\* This work is being carried on under "The Crane Research Fund for the Study of Allergic Diseases in Children."

\* Read at the Joint Annual Meeting of the American Association of Pathologists and Bacteriologists and the American Association of Immunologists, Chicago, March 28, 1929.

1. Longcope, W. T.; O'Brien, D. P., and Perlzweig, W. A.: The Antigenic Properties of Extracts of Horse Dander: I. Active Sensitization of Guinea Pigs to Horse Dander Extract, *J. Immunol.* **10**:599, 1925.

2. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: The Anaphylactogenic Character of Horse Dander and Its Crossed Relationship to Horse Serum, *Proc. Soc. Exper. Biol. & Med.* **23**:16, 1925.

3. A number of years ago we learned the importance of being certain of the source from which animals are secured, especially when working with horse serum.



substance to which they were originally sensitized. In no instance was an animal used in which sensitization was not established.<sup>4</sup> Thus fifty-nine animals were eliminated from our protocols, for these animals would have invalidated any interpretation of a crossed reaction.

On the day of the experiment, the horse serum and dander<sup>5</sup> extract were run through a Berkefeld filter; the diphtheria antitoxin was that distributed by the New York City Department of Health for intravenous therapy.

Throughout our experiments the horse serum, dander extract and diphtheria antitoxin were controlled by the method of specific anaphylaxis. In all instances of death, necropsies were performed and deaths through anaphylaxis were acceptable only when the lungs remained fully ballooned after the wall of the chest was opened. All the instances regarded as definite anaphylaxis were of the severe type, demonstrating the following symptoms: marked dyspnea, convulsions, collapse, suffusion of the eyes, severe scratching and coughing. The instances of moderate anaphylaxis were those manifested merely by varying degrees of dyspnea.

Early in our work we learned that dander extract may have a primary toxic effect<sup>6</sup> if injected intravenously in amounts over 2 cc., and we therefore have in no instance given an animal an intravenous injection of more than 1 cc., the majority having received 0.5 cc. The same amounts of horse serum and diphtheria antitoxin were given.

*Series I: Sensitizing Injection of Horse Serum—Crossed Shock Injection Dander Extract.*—GROUP 1.—In this first group were guinea-pigs of different sizes that had received injections of horse serum at various times. The sensitizing injections varied from 0.2 to 10 cc. and were given either intraperitoneally or intravenously. After an incubation period of from several weeks to seven months, each animal received an intravenous injection of dander extract, ranging from 0.5 to 1 cc. The animals that survived this injection of dander were given from 0.5 to 1 cc. of horse serum intravenously about one hour later, in order to prove that they were originally sensitized to horse serum.

There were sixty-five animals in this group. Only two of these died in typical anaphylactic shock and five showed definite symptoms after the shock injection of dander extract; in other words, seven animals showed a crossed reaction when injections of horse serum were made as a sensitizing agent and horse dander extract as the shock agent.

Forty-seven animals that gave negative reactions after the injection of dander extract died in typical anaphylactic shock after the subsequent injection of horse serum. Eight of the eleven that remained showed marked anaphylaxis with recovery, and three showed only moderate symptoms.

To summarize, of sixty-five animals sensitized to horse serum, only seven showed crossed anaphylaxis after receiving injections of dander extract; fifty-eight did not demonstrate this crossed relationship. It is suggested by this group, therefore, that crossed anaphylaxis between horse serum and its homologous dander is difficult to demonstrate.

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4. Ratner, B., and Gruehl, H. L.: *Investigations of Methods in the Study of Anaphylaxis*, Proc. Soc. Exper. Biol. & Med. **26**:197, 1928.

5. Many different samples of horse dander were obtained from the Park Riding Academy at many different seasons of the year.

6. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: *Respiratory Anaphylaxis*, Am. J. Dis. Child. **34**:23 (July) 1927.

GROUP 2.—There were eighteen animals in this group, weighing between 300 and 350 Gm. Each was sensitized by an intraperitoneal injection of 0.1 cc. of undiluted normal horse serum on Sept. 15, 1925. On October 2, seventeen days later, each received an intravenous injection of 1 cc. of dander extract. Two animals showed anaphylaxis with recovery; sixteen gave negative reactions. One hour later each received an intravenous injection of from 0.1 to 0.5 cc. of horse serum, and all died in typical anaphylactic shock.

Group 2, therefore, consists of a series of eighteen animals of practically uniform weight which were sensitized alike with small amounts of horse serum. Only two exhibited the crossed relationship to a moderate degree.

GROUP 3.—In this group there were thirteen animals, weighing between 350 and 500 Gm. Each received an intraperitoneal injection of 5 cc. of horse serum on June 8, 1928. On August 3, approximately two months later, each was given

TABLE 1.—*Crossed Anaphylaxis Between Horse Dander and Horse Serum*\*

Number	Ip. Sens. Injection with DE, Cc.	Incubation Period	Result After Injection of 1 Cc. of HS, Iv.	Result After Injection of 1 Cc. of DE, Iv.
1.....	0.5	9 weeks	Death	—
2.....	1.5	9 weeks	Death	—
3.....	1.0	9 weeks	Death	—
4.....	1.0	9 weeks	Death	—
5.....	0.5	1 month	Death	—
6.....	0.5	9 weeks	Death	—
7.....	0.5	1 month	Death	—
8.....	0.2	16 days	Anaphylaxis with recovery	Positive uterine horn reaction
9.....	1.0	7 weeks	Anaphylaxis with recovery	Death
10.....	1.0	9 weeks	Anaphylaxis with recovery	Death
11.....	1.0	9 weeks	Anaphylaxis with recovery	Death
12.....	0.2	16 days	Moderate anaphylaxis	Death
13.....	1.0	6 weeks	Moderate anaphylaxis	Death
14.....	1.0	6 weeks	Moderate anaphylaxis	Death
15.....	0.2	16 days	Negative	Death
16.....	1.0	27 days	Negative	Death
17.....	0.5	9 weeks	Negative	Death
18.....	1.5	6 weeks	Negative	Death

\* The weight of the animals when sensitized was from 250 to 300 Gm.; when given the shock injection, from 350 to 500 Gm. DE represents alkaline extract of horse dander; HS, normal horse serum; Iv., intravenously; Ip., intraperitoneally; Sens., sensitizing; death, typical anaphylactic death with the lungs completely ballooned. These experiments were carried out in the fall of 1925.

an intravenous injection of 1 cc. of dander extract. Seven of these animals gave negative reactions, three showed definite signs of anaphylaxis with recovery (dyspnea, convulsions, collapse) and three showed moderate signs of anaphylaxis with recovery (moderate dyspnea). One hour later, each received 0.5 cc. of horse serum intravenously, and all showed typical anaphylactic shock; nine died and four recovered.

In group 3, animals were sensitized with fifty times the sensitizing dose of the previous group. A higher degree of crossed sensitivity was manifested, six of thirteen animals showing moderate anaphylaxis.

*Series II: Sensitizing Injection Dander Extract—Crossed Shock Injection Horse Serum.*—In this group we reversed the order. The sensitizing injection was dander extract and the shock injection, horse serum. These results are given in table 1.

Of a total of eighteen animals, therefore, seven died in acute anaphylactic shock and seven showed symptoms of anaphylaxis with recovery after the crossed injection of horse serum.

Crossed anaphylaxis was exhibited with such regularity when horse dander was used as a sensitizing agent and horse serum as a crossed shock agent that we did not deem it necessary to carry out as large a number of experiments as in the former series.

*Series III: Crossed Anaphylaxis with the Uterine Strip Method.*—Fifteen guinea-pigs, weighing about 200 Gm., were sensitized by intraperitoneal injections of 1 cc. of either horse serum or horse dander extract. After an incubation period of from one to two months, the uterine horn was removed and was suspended in a 250 cc. bath of oxygenated Locke's solution at 37.5 C.; after it had assumed a normal base line, 1 cc. of the crossed antigenic solution was placed in the bath.

Five animals were sensitized with horse serum and crossed with dander extract. All gave negative reactions to the addition of dander extract, but a positive contraction when horse serum was placed in the bath. In this group there was no evidence of a crossed reaction.

The remaining ten animals were sensitized with dander extract. Three gave a positive contraction when horse serum was placed in the bath. All gave a positive contraction on the addition of dander extract.

In every experiment, the uterine horn was finally tested with a normal uterine contractor—0.001 Gm. of ergamine acid phosphate—to demonstrate that the muscle was still contractile and also to show its normal maximal contraction.

In the accompanying illustration the tracing shows the crossed reaction to horse serum of the uterine strip of an animal sensitized to horse dander. Several interesting points can be gathered from an analysis of this tracing. In the first place, it will be noted that when the crossed antigenic substance—horse serum—was placed in the bath, there was a definite contraction. After the base line was again established and the muscle had contracted normally for about sixteen minutes, dander extract was placed in the bath and an immediate uterine contraction was again manifested. This suggests that the first contraction to horse serum, owing to the common antigen present in horse serum and horse dander, did not bring about desensitization to the remaining antigenic elements in the horse dander. When the base line was reached after this contraction, ergamine was added to elicit a maximal contraction.

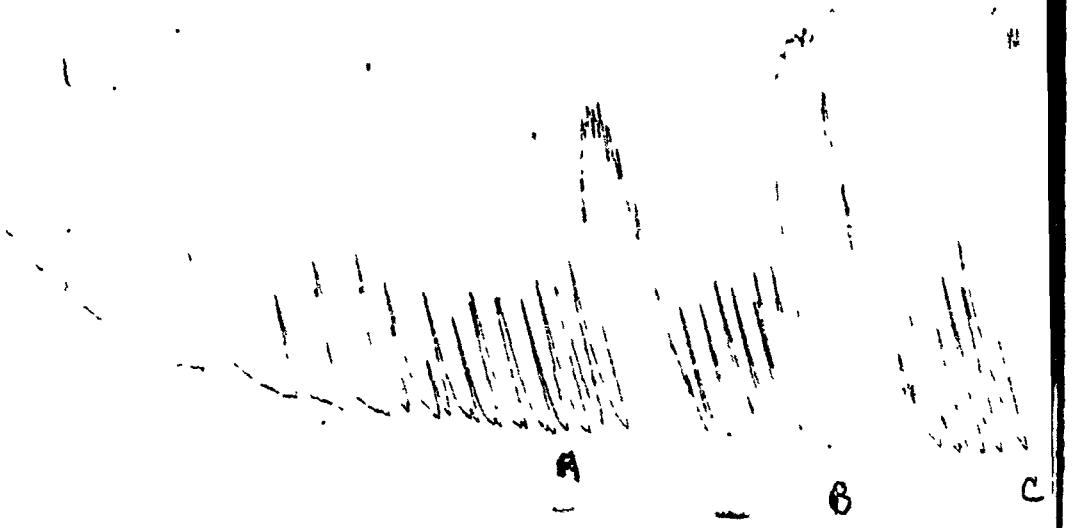
We did not continue further Dale experiments, for we believe that the Dale method is not as dependable as the intravenous route for determining a given state of hypersensitiveness.<sup>4</sup>

*Series IV: Sensitization to Horse Dander—Crossed Shock Injection Diphtheria Antitoxin.*—In order to show the position of antitoxin in this crossed relationship, the following experiments were carried out in the summer of 1928.

There were nineteen animals in this series, weighing between 300 and 400 Gm. Fourteen animals were sensitized with 0.5 cc. of dander extract intravenously and five with 5 cc. of dander extract intraperitoneally. The incubation periods varied

from nineteen days to four and one-half months. As a crossed shock injection, these animals received 0.5 cc. of diphtheria antitoxin intravenously. Two animals died in typical anaphylactic shock. These two were from the group previously noted with the large sensitizing injections and received injections after incubation periods of one and two months, respectively. Six animals manifested moderate

#439 (460 gms)  
 8/7/25 sensit.  $\bar{c}$  1 c.c D.E sp  
 10/16/25  
 A. T.C.C. H.S.  
 B. T.C.C. D.E.  
 C. 0.001 gm Ergamine



Virgin female guinea-pig sensitized by an intraperitoneal injection of 1 cc. of dander extract (DE); two months later, animal was killed by blow over the head and the Dale experiment performed. *A* represents the reaction to 1 cc. of horse serum; *B*, the reaction to 1 cc. of dander extract (DE), and *C*, the reaction to 0.001 Gm. of ergamine acid phosphate.

symptoms of anaphylaxis. The eleven remaining animals showed no crossed relationship after the injection of antitoxin. One hour after this injection all of the animals still alive were given an injection of dander extract intravenously; eleven died in acute anaphylactic shock and six showed definite anaphylaxis with recovery.

Two of the nineteen animals died of shock and six showed moderate anaphylactic symptoms when sensitized with horse dander and given a shock dose of diphtheria antitoxin. The two that died had received the large sensitizing dose.

In order to demonstrate whether animals sensitized to horse dander dust by inhalation would give crossed anaphylactic reactions with horse serum, the following experiments were made.

*Series V, Group 1: Nasal Sensitization with Dry Horse Dander—Shock Injection Horse Serum.*—Thirteen animals were sensitized by the inhalation of dry horse dander. They were placed in the special "dust chamber" for a total of eleven hours from April 27 to May 4, 1926. On May 26, one month after the initial exposure, the animals were given intravenous injections of from 0.5 to 1 cc. of horse serum. Five showed only moderate symptoms of anaphylaxis after the crossed injection. One hour later, after an intravenous injection of 0.5 cc. of dander extract, four died in typical anaphylactic shock, and the fifth showed only moderate symptoms of anaphylaxis with recovery. Six of the remaining animals, all of which gave negative reactions after the injection of horse serum, died in typical anaphylactic shock and two manifested definite anaphylaxis with recovery after the injection of dander extract.

*Group 2: Nasal Sensitization—Respiratory Anaphylaxis (Asthma) Followed by Crossed Injection of Horse Serum.*—In this group there was a series of thirty animals, weighing approximately 350 Gm. each, which had been placed in the dust chamber for their initial sensitization to dry horse dander dust. They were exposed for from seven to eleven hours over a period of two weeks and were then permitted to live in a normal environment for from one to two months. After this incubation period, the animals were again placed in the dust chamber, and in all instances they demonstrated definite respiratory anaphylaxis (asthma). These animals were then each given an intravenous injection of 1 cc. of horse serum; one animal, No. 1013, showed marked dyspnea with moderate collapse and recovery, and seven animals showed only suggestive symptoms of crossed anaphylaxis. One hour later, each received injections of 0.5 cc. of dander extract. Animal 1013 showed the same marked symptoms; six of the seven that showed a suggestive crossed reaction died, and one manifested marked anaphylaxis with recovery after the injection of dander. Eleven of the twenty-two remaining animals died in typical anaphylactic shock, four showed marked symptoms, two showed moderate symptoms and five gave negative reactions.

In order to determine the influence of repeated attacks of respiratory anaphylaxis to horse dander dust on the degree of crossed hypersensitiveness, a series of eighteen animals was used. Of this series, only two showed moderate evidence of this crossed relationship. As the results are comparable to the original group, we do not feel it necessary to quote the protocols in full.

These animals, which exhibited definite respiratory anaphylaxis to horse dander dust, showed only a suggestion of crossed anaphylaxis to horse serum.

*Series VI, Group 1: Nasal Sensitization—Crossed Injection of Diphtheria Antitoxin.*—Twenty-two animals, weighing between 200 and 350 Gm., were exposed to dander for one hour daily in the dust chamber for from six to twelve hours. One month later, they were each given an intravenous injection of 0.5 cc. of diphtheria antitoxin.

In only two instances was there moderate dyspnea after the injection of antitoxin and both of these animals died after an injection of 0.2 cc. of dander extract. The remaining twenty animals gave negative reactions to the crossed injection, and after a subsequent injection of 0.2 cc. of dander extract ten died in acute anaphylactic shock, five showed marked anaphylaxis with recovery and five, moderate symptoms of anaphylaxis.

*Group 2: Nasal Sensitization—Respiratory Anaphylaxis—Crossed Injection of Diphtheria Antitoxin.*—Fifteen animals were sensitized by daily exposures of one hour each to dander dust for a total of eleven hours, beginning on Nov. 21, 1927. Five weeks later, when exposed in the dust chamber, they showed definite symptoms of respiratory anaphylaxis.

From three to eight weeks after their last contact with the dry dander they received an intravenous injection of 0.5 cc. of diphtheria antitoxin. Two animals showed a suggestion of crossed anaphylaxis and died after a subsequent injection of 0.5 cc. of dander extract.

One animal (420 Gm.) manifested severe respiratory anaphylaxis in the dust chamber and, four weeks later, after an intravenous injection of 0.5 cc. of diphtheria antitoxin died in typical anaphylactic shock with complete ballooning of the lungs.

The remaining twelve animals gave negative reactions after the crossed injection, but were proved to be highly sensitive to dander for all died in typical anaphylactic shock after an injection of dander extract.

*Group 3: Nasal Sensitization—Repeated Attacks of Respiratory Anaphylaxis—Crossed Injection of Diphtheria Antitoxin.*—In this final group there were twenty animals, weighing between 250 and 300 Gm. when initially sensitized and about 600 Gm. when receiving final injections. These animals were subjected to repeated contacts with horse dander in the dust chamber after they had been originally sensitized by inhalation. They manifested varying degrees of respiratory anaphylaxis at different times, and all received an intravenous injection of 0.5 cc. of diphtheria antitoxin from two to six months after their initial contact with dander.

Fifteen of this group gave negative reactions to the crossed injection. One animal, however, showed definite collapse with recovery, and four animals manifested moderate symptoms of anaphylaxis after the crossed injection. Four of these five animals died in typical anaphylactic shock and the fifth manifested definite anaphylaxis with recovery after the subsequent intravenous injection of dander extract. The fifteen animals that gave negative results after the crossed injection were proved highly sensitive by either death or severe anaphylactic symptoms after the injection of dander extract.

To sum up, of a total of fifty-seven animals sensitized to horse dander dust, nine showed varying degrees of crossed anaphylaxis and one died in anaphylactic shock after receiving injections of diphtheria antitoxin.

## COMMENT

The foregoing protocols present a series of experiments in which we have studied the crossed anaphylactic relationship between horse dander and its homologous serum. The experiments are divided into six series.

In series I, there are three groups with a total of ninety-six animals. These animals received a sensitizing injection of undiluted normal horse serum, and after varying incubation periods received their second or shock injection of dander extract. There were only two deaths from this crossed injection of dander; ten animals showed definite crossed anaphylaxis and three, moderate anaphylaxis, making only fifteen positive crossed reactions from ninety-six animals.

It is interesting that the two animals that died had been given a rather large sensitizing dose. In the second group, in which we used a rather small sensitizing dose, there were fewer crossed reactions than in group 3 in which a larger sensitizing dose was used.

Series II, however, presents a strikingly different situation. When animals were sensitized to dander extract, it seemed to be much easier to produce a crossed reaction with horse serum. In this series there were eighteen animals, of which seven died in typical anaphylactic shock after the crossed injection, four showed definite anaphylaxis, three moderate symptoms and four gave negative reactions.

Series III graphically demonstrates by the Dale method the existence of this crossed relationship.

In series IV, the crossed relationship between dander sensitization and diphtheria antitoxin was studied. Here, too, is evidence that crossed reactions can be elicited, for two animals died of acute anaphylactic shock and six showed moderate symptoms after the crossed injection of diphtheria antitoxin. The two animals that died had received a large sensitizing dose.

In series V there are three groups, totaling sixty-one animals which were sensitized through the inhalation of dry horse dander. Of this series, only two showed a definite crossed reaction with horse serum, five showed moderate symptoms and eight gave suggestive reactions.

In the final series, we studied the crossed relationship between horse dander inhaled as an antigen and diphtheria antitoxin injected as a shock agent. Fifty-seven animals were sensitized nasally, and of these one died in typical anaphylactic shock after an injection of antitoxin. One animal showed marked anaphylaxis with recovery, six manifested moderate symptoms and two were only suggestive.

Table 2 summarizes the results of our experiments.

The statement of Longcope and his co-workers<sup>1</sup> that horse dander is specifically antigenic and bears no crossed relationship to horse serum is untenable. Our statement, appearing almost simultaneously in pre-

liminary form, that there is a crossed relationship appears to be correct, for Forster,<sup>7</sup> who has recently repeated these experiments, has found such a crossed relationship definitely to be present.

The outstanding peculiarity that we found early in our work was the fact that sensitization to horse serum and crossed shock reaction to horse dander was rarely consummated, whereas when animals were sensitized to horse dander, a much greater number gave a crossed reaction after an injection of horse serum. It is gratifying to note that Forster, with crossed precipitation reactions, found a much higher titer of crossing when antidander serum was used with horse serum as antigen than when antiserum against horse serum was titrated against horse dander. Forster's experiments with anaphylaxis in the animal bring out this peculiarity, for of twelve animals sensitized to horse dander, ten were fatally shocked by a crossed injection of horse serum, whereas of fifteen animals sensitized to horse serum, only three gave suggestive crossed

TABLE 2.—*Crossed Anaphylactic Relationship Between Horse Dander and Horse Serum*

Sensitizing Substance	Shock Substance	Total Number of Animals	Positive	Negative
Horse serum.....	Dander extract	96	15	81
Dander extract.....	Horse serum	18	14	4
Dander extract.....	Antitoxin *	19	8	11
Dander dust †.....	Horse serum	61	15	46
Dander dust.....	Antitoxin	57	10	47

\* Antitoxin: New York City Department of Health diphtheria antitoxin.

† Dander dust: guinea-pigs sensitized by inhaling dry dander dust in "dust chamber."

reactions with horse dander. This relationship seems to be fairly definite.

We maintained that the final criterion for anaphylactic experimentation cannot rest with the uterine strip method. Our protocols show that fourteen of eighteen animals sensitized to horse dander manifested a crossed reaction to the injection of horse serum, whereas with the Dale method there were only three positive crossed reactions in ten animals sensitized to horse dander. It is curious to note that Forster obtained only two positive crossed reactions with the Dale method out of seven tests and showed ten positive crossed experiments with twelve animals receiving injections. These results are practically identical with ours. Since Longcope based his conclusions on only a few Dale experiments, this probably accounts for his failure.

The common factor resident in horse dander and horse serum is presumably present in very small amounts and is related to the globulins, for we had animals sensitized to horse dander that could be killed by an

7. Forster, G. F.: Is There an Immunological Relationship Between Horse Serum and Horse Dander? J. Exper. Med. 47:903, 1928.



injection of diphtheria antitoxin. This antitoxin contains only pseudoglobulins.<sup>8</sup>

It has been noted by one of us (B. R.) that persons naturally sensitive to horse dander are, in the minority of cases, sensitive to horse serum in varying degrees. Some of these, however, are exquisitely sensitive to horse serum, though they have never received a previous injection of horse serum. A direct corollary may be drawn between such persons and the guinea-pigs nasally sensitized to horse dander and shocked by horse serum antitoxin.

#### CONCLUSIONS

From our experiments we conclude that horse dander and horse serum are antigenically related, the common substance being present in small amounts and related to the globulin fraction. This common substance is apparently present in smaller amounts in the horse dander than in the horse serum, since it is easier to sensitize an animal to horse dander and cause shock with horse serum than the reverse. Desensitization does not occur after recovery from a crossed shock injection.

Nasal sensitization and respiratory anaphylaxis (asthma), induced in animals through the inhalation of dry horse dander, can result in horse serum hypersensitiveness, and such animals may be killed by an injection of horse serum antitoxic globulin.

It is suggested that this mechanism of natural sensitization to horse serum through the inhalation of horse dander is related to the problem of the hypersensitiveness of man to horse serum.

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8. Personal communication from Dr. Edwin J. Banzhaf, Research Laboratories, New York City Department of Health. The diphtheria antitoxin used in these experiments had had the albumin, euglobulin and fibrin removed and contained only the pseudoglobulins in a concentration of three times that found in normal horse serum. This antitoxin is heated to 58 C. for two hours. The antitoxin is distributed for intravenous administration.

# THE RETICULO-ENDOTHELIAL SYSTEM OF THE RABBIT\*

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The reticulo-endothelial system of the rabbit has been investigated by the introduction into the peripheral circulation of rabbits' red blood corpuscles stained with iron hematoxylin. Charles Bolton<sup>1</sup> used corpuscles stained with Ehrlich's acid hematoxylin in his study of absorption from the peritoneal cavity. The advantages of the use of corpuscles in the present study were that the injected particles were of uniform size, were normal inhabitants of the blood vessels and were easily identified in their ultimate situations. When care was taken in the preparation of the black erythrocytes, a suspension of them was obtained in normal solution without clumping.

## EXPERIMENTAL WORK

Blood was aspirated from the rabbit's heart. It was defibrinated by whipping, and centrifugated. The serum was then pipetted off, and alternately washed with saline solution and centrifugated. Mordanting was performed with 2 per cent ferric alum for thirty minutes, and the preparation was allowed to stand overnight. It was then alternately washed with saline solution and centrifugated. For staining, 0.5 per cent aqueous hematoxylin was applied for thirty minutes or more. This was followed by alternate washing with sterile saline solution, and centrifugation. The corpuscles were fixed in 1 per cent formaldehyde for one hour. They were then washed with sterile saline solution and centrifugated. Sterile saline solution was added in the required amount.

During the mordanting and staining, it was found advisable to work with thin suspensions of cells in order to prevent clumping. The cells of the suspension could be counted in the same way as the cells of blood are counted, by a hemacytometer.

The saline suspensions of black erythrocytes were injected into the marginal veins of the ears of both normal and splenectomized rabbits. The animals were killed at periods varying from two hours to one week after the injection.

The number of cells injected varied from 1,000,000 to 121,000,000. The average rabbit erythrocyte count is about 7,000,000 per cubic millimeter. The ultimate destination of the black cells was the same whether a smaller or a larger number of cells was injected. The animal that received the largest number of cells died of pneumonia two days later, while another animal receiving 46,000,000, which was killed a

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\* Submitted for publication, May 21, 1929.

\* From the Department of Pathology, Moukden Medical College, Manchuria.  
1. Bolton, Charles: *J. Path & Bact.* **24**:429, 1921.

week later, presented by no means such numerous black cells as did the rabbits killed soon after the injection.

The length of time the black cells remained in the peripheral circulation was variable. Sometimes they disappeared quickly. In the case of the animal that had received 121,000,000 cells, there were still 4,687 per cubic centimeter twenty-four hours later. No "blood crises," such as Elvidge<sup>2</sup> recorded as following the intravenous injection of particles of quartz, india ink, carmine or trypan blue, were observed. In the animal that was allowed to live for a week after the injection, a noticeable increase of large mononuclear cells was present in the blood throughout this period, commencing during the second twenty-four hours.

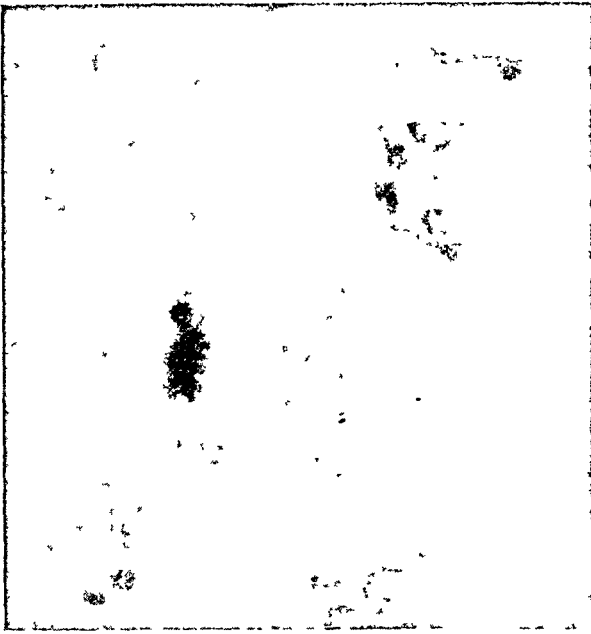


Fig. 1.—Kupffer cells of liver containing black erythrocytes

#### POSTMORTEM EXAMINATION

The liver and the spleen were invariably black. The lungs were also dark. No other organs showed any change of color. In the splenectomized animals, the liver and the lungs were the only organs to show changes of color.

In the normal animals, the liver, the spleen and the lungs took up most of the black cells. The Kupffer cells of the liver often contained large numbers of them (fig. 1). In the spleen, the cells were also taken up in large numbers by the reticulo-endothelial cells of the pulp. When the pieces of the spleen were embedded in paraffin, after dissocia-

2. Elvidge, A. R.: *J. Path. & Bact.* **29**:325, 1926.

tion in weak chromic acid, the cells lining the splenic sinuses appeared free of the black erythrocytes. They were absent, also, from the central part of the malpighian corpuscles.

It was difficult to determine in the lungs (fig. 2) what cells were responsible for the phagocytosis. In the alveoli there seemed to be three possible sources, the cells lining the alveoli, the endothelium of the capillary in the alveolar wall or histiocytes lying deep to the alveolar lining. Aschoff<sup>3</sup> said that ordinary endothelium did not have any place in the reticulo-endothelial system, and Maximow<sup>4</sup> said that the endothelium was not able to produce histiocytes. Lang,<sup>5</sup> quoted by Bloom,<sup>6</sup> studied



Fig 2.—Black erythrocytes phagocytosed by alveolar cells of lung (histiocytes?).

cultures from the lungs of rabbits in great detail. He traced the alveolar phagocyte to the septum cells. The latter, he believed, are partially differentiated mesenchymal elements within and on the alveolar wall, which under such stimuli as bacteria or dust particles or

3 Aschoff, L. Lectures on Pathology, New York, 1924, p 16.

4. Maximow, A. A.: Morphology of Mesenchymal Reactions, Arch. Path. 4:578 (Oct) 1927

5 Lang, F. J.. Arch. f. exper. Zellforsch. 2:93, 1926

6 Bloom, William: Immune Reactions in Tissue Culture: Reaction of Lungs from Normal and Immunized Rabbits to Pigeon Erythrocytes, Arch. Path. 3:613 (April) 1927.

explantation develop into alveolar phagocytes. Fried<sup>7</sup> concluded from an experimental study of the origin of histiocytes in the lungs by the use of intratracheal injections of vital stain, that (1) the phagocytes in the pulmonary alveoli in inflammatory and congestive processes are macrophages or histiocytes and therefore cells of mesenchymal origin; (2) that these cells originate from the nucleated cells commonly spoken of as the (respiratory) epithelial cells lining the wall of the pulmonary alveoli, and (3) that the so-called epithelial cells lining the pulmonary alveoli are to all appearances not epithelial, but of mesenchymal origin—that is to say, they are histiocytes and belong to the reticulo-endothelial system.

The fact that the lungs took such an important part in the phagocytosis of the injected black erythrocytes, only less important than the parts played by the liver and the spleen, and exceeding in importance the parts played by the bone-marrow and the lymphatic tissue, as will appear later, seems to lead to the conclusion that the lungs form an important part of the reticulo-endothelial system in the rabbit.

The bone-marrow was somewhat variable in its content of black erythrocytes, sometimes presenting a scanty number and sometimes many. They were never so numerous as in the liver, the spleen and the lungs.

The lymphatic glands, whether mesenteric or in other situations, and the appendix, a large lymphoid organ in the rabbit, took up practically no black cells. Occasionally, one or two cells were seen in a section, but often none at all.

The kidneys showed sometimes a considerable number of black erythrocytes, either situated in intertubular cells or in the glomeruli. Other organs occasionally examined were the suprarenal glands and the pancreas. These each contained a few of the cells.

It was only in the liver and the spleen that the cells were present in masses. Elsewhere the cells were phagocytosed singly or in small groups of two or three or four. This was true even of the lungs, although their total content of black cells was great. This seems to indicate either a difference in the avidity with which the cells in the various parts of the reticulo-endothelial system phagocytose the black erythrocytes or a difference in the size of these cells.

The distribution of the phagocytosed erythrocytes in the splenectomized animals was precisely the same as in the normal animals. The liver seemed capable of entirely compensating for the absence of the

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7. Fried, B. M.: Origin of the Histiocytes (Macrophages) in Lungs: Experimental Study by Use of Intratracheal Injection of Vital Stain, *Arch. Path.* **3**:767 (May) 1927.

spleen. Jaffé<sup>8</sup> stated that in several animals, such as the rabbit, mouse (M. B. Schmidt) and *Macacus rhesus* (Krumbhaar and Musser), the removal of the spleen caused a proliferation of the stellate cells of the liver. If this is the case, the compensation is easily accounted for, particularly as the spleen in the rabbit is a comparatively small organ.

The question arises whether the black erythrocytes are to be regarded merely as foreign bodies or as dead hemoglobin-containing blood cells. To determine this point, india ink was injected into the circulation of another rabbit, and its ultimate distribution compared with that of the black erythrocytes. It was found to be almost the same.

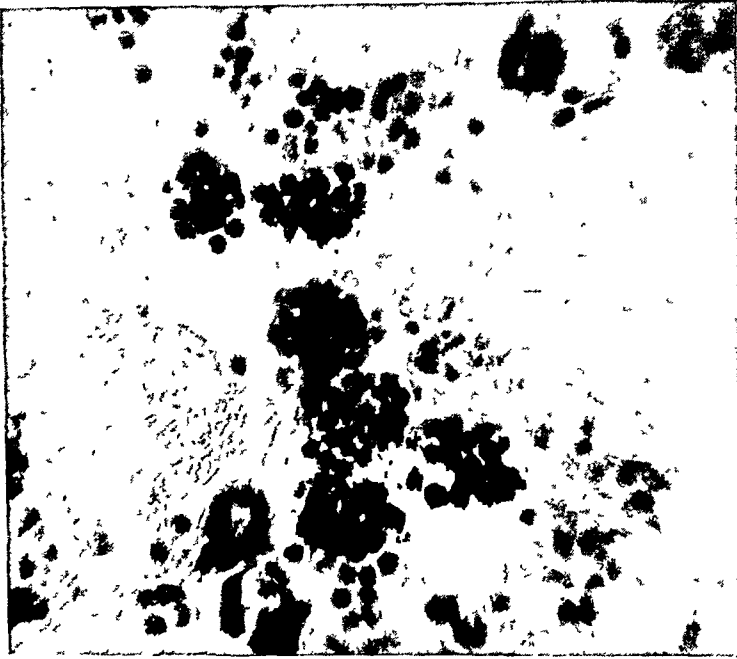


Fig. 3.—Cervical lymph gland, with multiple erythrocytes contained within the reticulo-endothelial cells of the lymph sinus.

The bone-marrow, however, was dark, unlike that of the animals which had received the injection of black erythrocytes. Microscopically, too, the carbon pigment was present here in great quantity in the reticulo-endothelial cells, although, for the most part, in small particles and in moderate amount in any one cell. Again, the lymphatic glands and the appendix were practically free of carbon particles, while the kidneys and the suprarenal glands contained them.

The mesenteric lymph glands of the rabbit are, to a considerable extent, hemolymph glands. They commonly contained many cells the protoplasm of which was full of phagocytosed red corpuscles. Vessels

<sup>8</sup> Jaffé, R. H.: Reticulo-Endothelial System; Its Rôle in Pathologic Conditions in Man, Arch. Path. 4:48 and 54 (July) 1927.

supported by a lymphoid sheath were not infrequent, reminding one of the lymphoid-sheathed arterioles of the spleen. Blood pigment was sometimes seen in these glands. These facts seem to point to a function analogous to that of the spleen. Even the cervical lymph glands of the rabbit helped on occasion in the destruction of the effete blood corpuscles (fig. 3). In a splenectomized rabbit, large numbers of fragmented polymorphonuclear cells were observed in the reticulo-endothelial cells of a cervical lymph gland. In this animal, these cells were also phagocytosed by the megakaryocytes of the marrow (fig. 4), so that these cells have other functions, in the rabbit, at any rate, than the formation of thrombocytes.

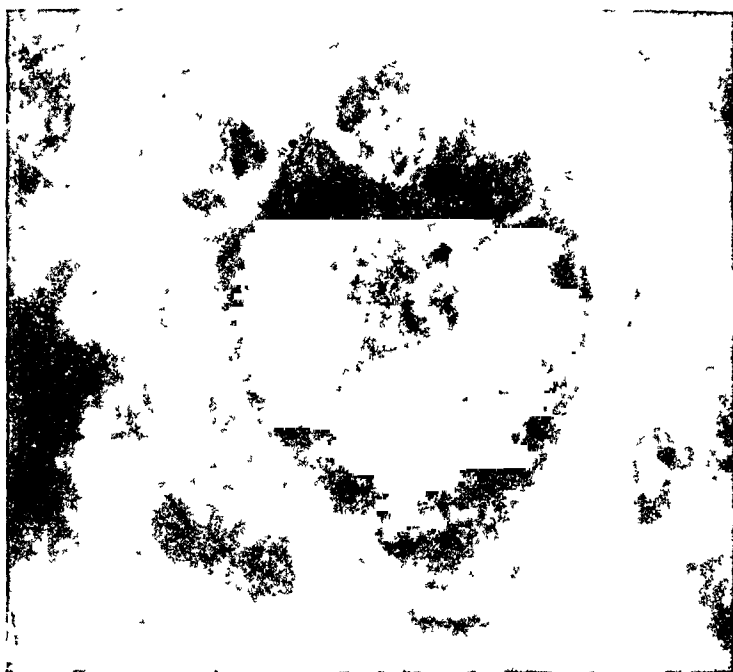


Fig. 4.—Megakaryocyte of bone-marrow containing three phagocytosed, partially digested polymorphonuclear cells.

The lymphatic glands of the rabbit, then, though playing an important part in the metabolism of blood pigment, did not seem to take any noticeable share in the phagocytosis of dead blood cells or of carbon particles injected into the peripheral circulation.

As has already been mentioned, the appendix, which in the rabbit is a large lymphoid organ, and the wall of which in the normal animal contains much pigment, also seemed to take no part in the phagocytosis of foreign particles injected into the peripheral circulation.

There seems to be, then, a differentiation of function in the various parts of the reticulo-endothelial system of the rabbit, and, where function is the same, a difference in ability to perform the function. Reference has already been made to the difference in numbers of

black erythrocytes taken up by the cells of the liver and the spleen, on the one hand, and by the cells of the lungs and other parts of the reticulo-endothelial system, on the other. There seems to be, also, a difference between the reticulo-endothelial cells lining the splenic sinuses and those of the pulp. It has already been stated that the cells lining the splenic sinuses did not take up the black erythrocytes. When india ink was injected into the circulation of the rabbit, although the spleen as a whole took up the carbon pigment in great quantity, this pigment was present in the sinus reticulo-endothelial cells in fine particles and in small amount, whereas in the cells of the pulp, the pigment was present in masses. It was difficult to make out this difference in the rabbit's spleen in sections prepared in the ordinary way, but when dissociation in weak chromic acid was carried out before the tissues were embedded, this could be clearly determined.

This difference in function in the various parts of the reticulo-endothelial system has been noticed in pathologic conditions in which blood is being destroyed. Jaffé<sup>8</sup> pointed out that while in infectious diseases the whole reticulo-endothelial system is usually involved in the process of destruction of erythrocytes, in the hemolytic anemias only certain organs show a predilection for the phagocytosis of erythrocytes. In pernicious anemia, as well as in hemolytic jaundice, the phagocytosis of red cells in the spleen is much less pronounced than it is in the other parts of the reticulo-endothelial system.

#### SUMMARY

A method of preparing rabbit's erythrocytes for injection into the circulation of other rabbits is described. The method makes them easily identifiable afterward.

Using this method, one finds that, in normal animals, the spleen, the liver and the lungs take up the major portion of the injected cells; the bone-marrow takes them up to a less degree, and other organs, such as the kidneys, suprarenal glands, etc., slightly; the lymphatic glands and the appendix take them up hardly at all. In splenectomized animals the distribution is the same.

The injected cells are phagocytosed in large numbers by the Kupffer cells of the liver, and by the cells of the splenic pulp, while they are taken up singly or in small groups by the reticulo-endothelial cells of the lungs, the bone-marrow and the other parts of the reticulo-endothelial system.

The importance of the lungs in the reticulo-endothelial system of the rabbit is pointed out.

Evidence is given showing that the lymphatic glands of the rabbit play an important part in the metabolism of blood pigment.



This distribution of the phagocytosed black erythrocytes and carbon pigment in the spleen, after injection into the peripheral circulation, is shown to differ in the cells lining the sinuses and in the reticulo-endothelial cells of the pulp.

On these grounds, two suggestions are made: that the various parts of the reticulo-endothelial system of the rabbit vary in function, and that the parts in which the functions are the same, are not equipotent.

# THE DEVELOPMENT OF A CARCINOMA OF THE BREAST

REPORT OF A CASE \*

HELEN INGLEBY, M.B., M.R.C.P.

PHILADELPHIA

*History.*—A single woman, aged 42, was admitted to Woman's College Hospital in the service of Dr. Margaret Sturgis. She complained of a tumor of the right breast of two months' duration. It was situated in the inner and upper quadrant, and when first noticed was the size of a peanut. The menses were regular. The last menstrual period had begun on Nov. 27, 1928. The operation took place on Dec. 21, 1928, i. e., four days before the next period was due. The past history of the patient was unimportant. Her mother had died of carcinoma of the breast at the age of 39.

On admission, a hard tumor the size of an egg was found in the upper inner quadrant of the right breast.

The tumor was excised locally and reported on at once. Halstead's operation for removal of the breast was then carried out.

*Macroscopic Examination.*—The main growth measured about 2 by 3 cm., and was densely adherent to the surrounding breast tissue. It felt hard and cut "like an unripe pear." The breast itself was rather nodular. A small, hard nodule, the size of a millet seed, was found near the muscle, and proved to be a secondary growth. Paraffin sections were made from the main tumor and from various parts of the breast and stained with hematoxylin and eosin. Three of four sections of breast showed growth, and metastases were present in the glands.

*Microscopic Examination.*—The main tumor consisted of atypical, more or less polygonal cells with irregular nuclei, most of which stained moderately deeply. Mitotic figures were numerous. There was little fibrous tissue but enormous numbers of small round cells, mainly lymphocytes. The malignant cells appeared to have developed in ducts, and remains of distended ducts could be seen around most of the clumps. The tumor shaded off into normal breast tissue showing the typical premenstrual phase of proliferation. This part of the section was particularly interesting because in it the transition of physiologic proliferation into carcinoma could be clearly followed.

In the unaffected lobules, the ductules showed the following normal characters (fig. 3): They were lined by relatively small, more or less cuboidal cells, in each of which the nucleus occupied the greater part of the cell. The nuclei were somewhat irregular in size and shape. Most of them were oval, the long axis of the nucleus being at right angles to the duct. For the most part, they stained deeply owing to the dense, fine, chromatin meshwork that they contained. In the resting state, the nuclei were small and stained deeply. As the premenstrual phase was approached, they enlarged, the chromatin meshwork was spread apart and therefore the whole nucleus appeared lighter. For this reason, the largest

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\* Submitted for publication, May 31, 1929.

\* From the Department of Pathology of the Woman's Medical College of Pennsylvania.

nuclei in our sections of normal ductules tended to appear pale. They also lost their characteristic shape and became round. The nuclear membrane was always well defined, and there was usually a fairly definite nucleolus. The protoplasm was scanty, except when premenstrual secretion was actually going on, and then the cell was seen to be columnar, the protoplasm being collected toward the lumen. The cell outlines were not clear. The nuclei were basal and close together, often nearly touching each other. Sometimes their arrangement was a little irregular, and in the larger ductules more than one layer of cells was usually visible. The

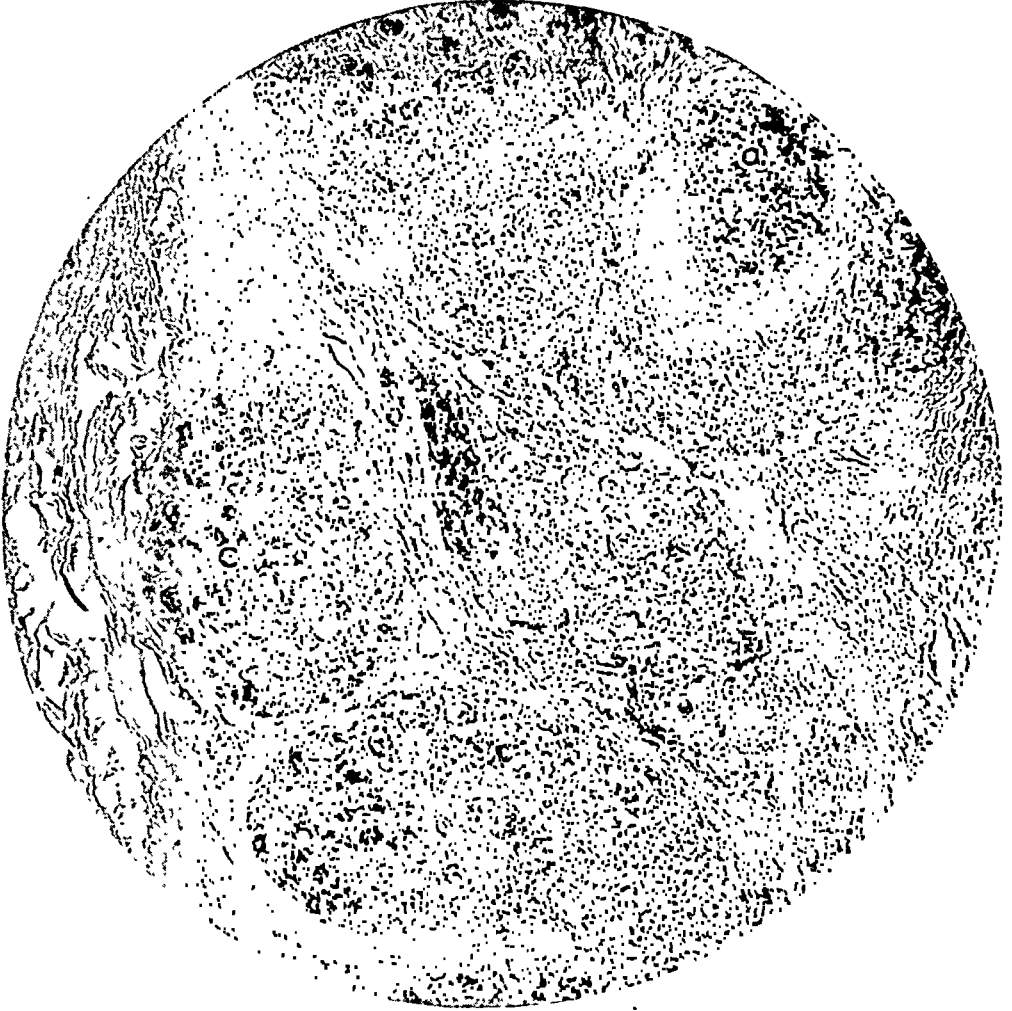


Fig. 1.—A photomicrograph of tumor of the breast, showing (a) a distended duct filled with carcinoma cells, and (c) a lobule in the premenstrual stage of development.

cells of the basement membrane participated in the premenstrual growth, the nuclei being ovoid and plump and the protoplasm sometimes a little vacuolated. Around each duct was a narrow band of hyaline connective tissue. This became broader and more conspicuous the nearer the ductules were to the tumor. Spaces between them were filled with loose, rather edematous, fibrillary meshwork. In some areas, the ductules showed a wider lumen than in others, and some contained secretion.

The first sign of a malignant change was an increase in the size of the cells lining the ductules. Figure 4 shows the earliest changes that could be detected. The chief abnormality was that the nuclei of some cells, although not larger than those often found in the premenstrual breast, were larger than any seen in the normal ductules of this particular specimen. They were unduly pale and a little irregular in outline. This alone would not class them as carcinomatous. I have seen similar cells in other breasts in the late premenstrual phase. More significant, taken in conjunction with these observations, was the broad band of hyalin

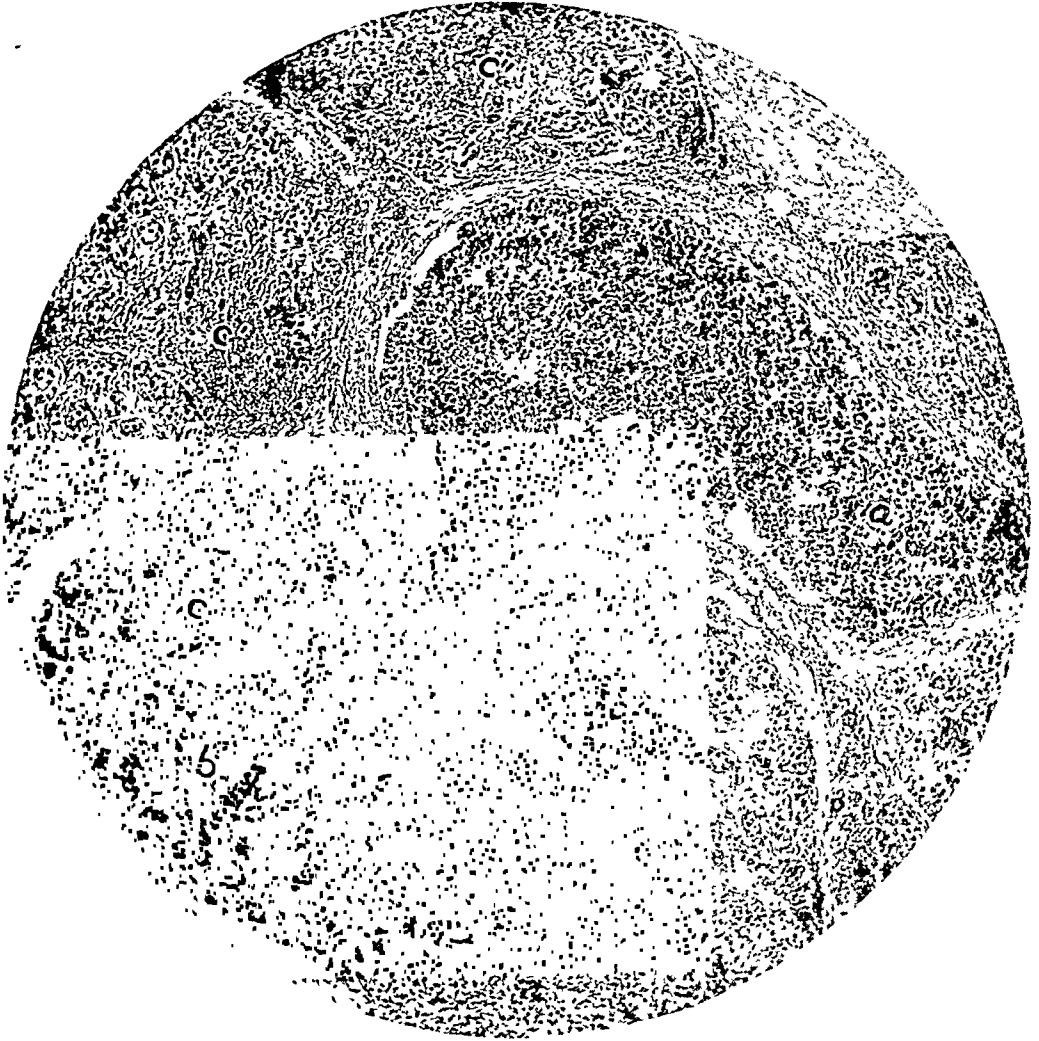


Fig. 2.—A photomicrograph of tumor of the breast showing a distended duct (*a*) filled with carcinoma cells down to its terminal branches (*b*), which are ending in the lobule (*c*). Some ductules in *c* are carcinomatous, others are not. *a'* indicates a similar carcinomatous duct; *c'* and *c''*, other partly carcinomatous lobules.

that surrounded the ductule. The periductal fibrous tissue degenerated in the breast *pari passu* with proliferation of the epithelium, and the broad band of hyalin probably represented excessive degeneration and compression of this surrounding connective tissue.

In figure 5, a ductule is shown in which the lesion had progressed a step further. All the cells were hypertrophied, and the two largest would have been



Fig. 3.—A normal premenstrual ductule from a noncancerous part of the breast operated on for tumor.

Drawings 3 to 6 were made with camera lucida under  $\frac{1}{12}$ " Zeiss oil immersion; no. 4 eyepiece; tube length, 140 mm.

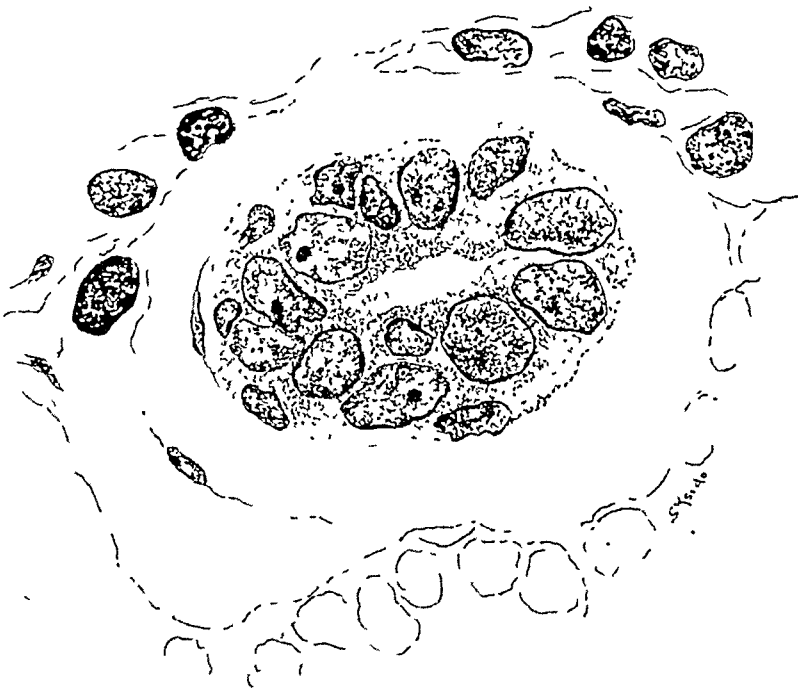


Fig. 4.—Small ducts in a lobule, the main duct of which was filled with carcinoma cells. This ductule shows the earliest changes that could be detected, i. e., commencing hypertrophy of cells and widening of the hyaline band around the ductule.

abnormal for any stage of the sexual cycle. Figure 6 shows a ductule lined by these large cells. The architecture here appeared almost normal; but, owing to the size of the individual elements, no more than four or five surrounded a lumen where normally there would be eight or ten. In most cases, however, the cells had grown at different rates, and the resulting irregularity of size, with compression of some cells, made the abnormality conspicuous (fig. 5). At this stage, the nuclei were often more than twice the normal size. Although many of them were oval as in normal areas, irregularity of contour began to be a marked



Fig. 5.—An early stage of carcinomatous hypertrophy in a small duct. The ductule was situated in a premenstrual lobule, the main duct of which was the site of malignant growth. The carcinoma in the duct had not reached this part of the lobule, which itself was undergoing malignant proliferation. The drawing shows (1) an irregular overgrowth of the epithelial lining, (2) hypertrophy of the cells of the basement membrane and (3) a wide hyaline band around the ductule.

feature. This, as has been said, may occur in nuclei of premenstrual ductules in noncancerous breasts, but never to the same extent. That the lesion was an overgrowth of preexisting cells seemed to be confirmed by the fact that the spaces in the chromatin meshwork of the nuclei were much larger; i. e., they appeared to be distended by an increase of the colorless material. In some cells,

it looked as though the chromatin threads had given way and retracted, just as elastic fibrils retract when ruptured, and in consequence the nucleus was left stippled with dots of chromatin to which threads were sometimes seen hanging. In the earliest stage, the chromatin seemed to increase in amount with the size of the cell, and it is possible that in some cells this increase continued. But, for the most part, deeply staining tumor cells were seen only where cell division had certainly taken place. As the figures show, abnormal growth was not confined to the lining epithelium, but also affected the cells of the basement membrane. The surrounding hyaline band was now broader; as a rule, it was still present in the next stage.



Fig. 6.—A carcinomatous overgrowth of cells in a ductule. The architecture of the ductule is still preserved, but only four cells surround the remains of the lumen. These have reached approximately the limit of their growth. After this stage, they divide or degenerate.

The next phase was that of degeneration or division of the swollen cells, presumably when the cubic contents became too great for the surface area; i. e., when the cell was too large to go on receiving nourishment. In these areas, the normal architecture of the ductules was lost. They became converted into groups of large, irregularly polygonal cells, generally with pale but sometimes dark nuclei; mitoses were numerous.

The carcinoma cells just described arose directly from ductules belonging to lobules that were formed during the course of the sexual cycle. In the larger ducts, a different type of growth was present. The tumor cells were smaller and, if anything, more irregular; they stained more deeply, and the nuclei tended to be elongated, sometimes triangular (this probably represented an attempt at

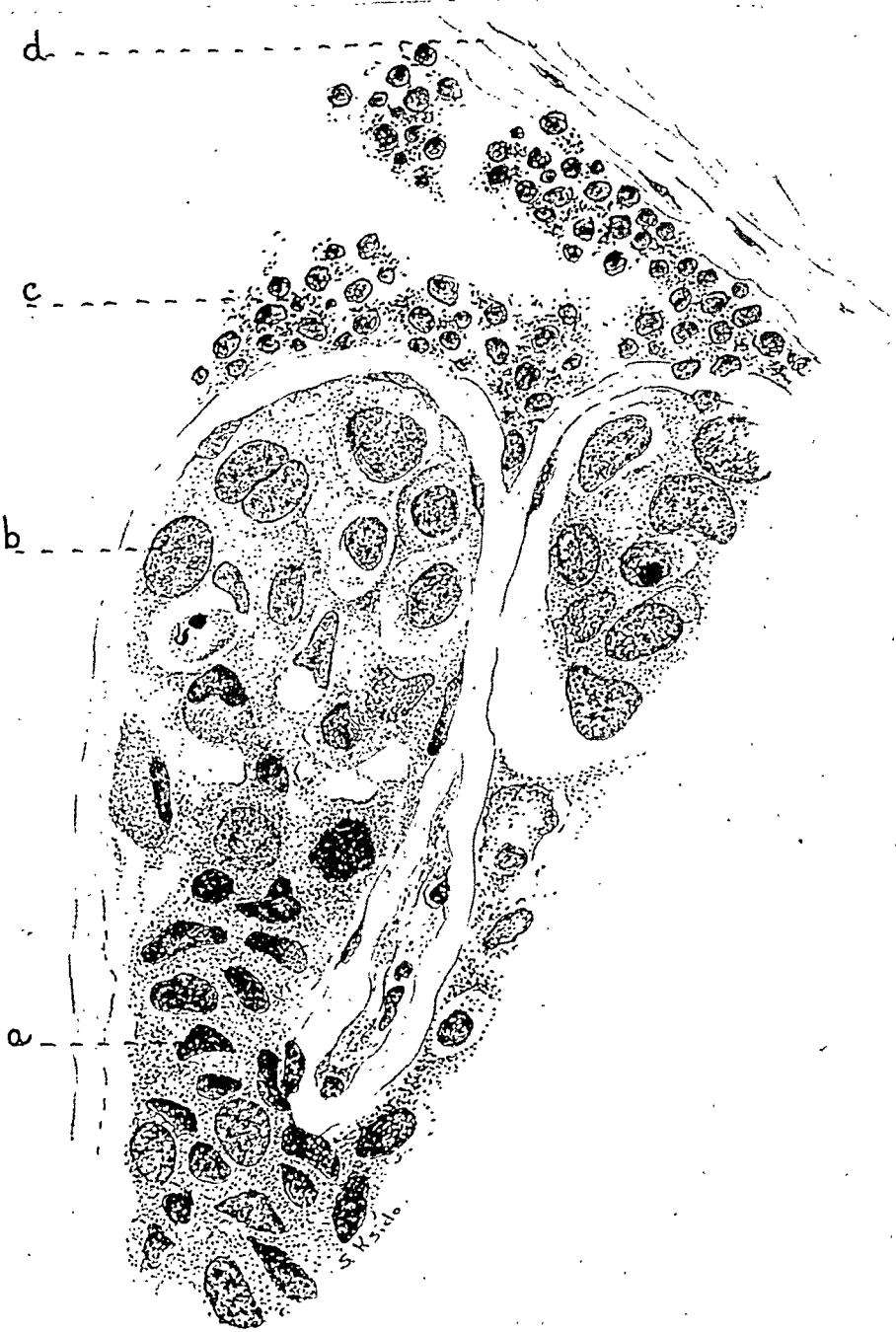


Fig. 7.—The terminal portion of a ductule showing the two varieties of carcinoma cells lying side by side: *a*, carcinoma cells invading a lobule from the main duct; *b*, carcinoma cells arising from the epithelium of the terminal portion of the ductule; *c*, a lymphocytic infiltration, and *d*, outer margin of the lobule.

This figure was drawn with camera lucida under  $\frac{1}{12}$ " Zeiss oil immersion; no. 1 eyepiece; tube length, 140 mm.



duct formation). The nuclei showed the remains of a meshwork, but it was irregular and often not present. The change in cell type was evidently the result of rapid, irregular division and of mechanical pressure rather than a fundamental difference. These cells grew centripetally along the ducts, and as the ducts narrowed they became elongated. Finally some of the ductules were invaded by them. The two types of cell then lay side by side (fig. 7).

*Comment.*—Although one is dealing here with a transformation of cells of lobules into carcinoma, the primary lesion was certainly in the ducts. Wherever the lobule was affected by carcinoma, the duct leading to it was seen to be full of carcinoma cells. The lesion was evidently spreading from ducts to lobules. Figure 2 shows this in almost diagrammatic fashion. The growth of carcinoma cells in the ducts did not quite keep up with premenstrual proliferation, but the lobules had caught the infection, if one may put it that way, or better, were stimulated to undergo malignant changes.

The difference in cell type in the ducts and lobules may be due to the difference in origin of the cells or to the fact that the more carcinoma cells divide, the more atypical they become. The latter explanation is probably correct, for it is to be expected that the duct cells, which had been dividing for some time, would be more undifferentiated than the lobule cells, which were only just becoming carcinomatous.

This case gives some indication of the mode of spread of malignant disease and suggests that the varied appearances presented by the cells in different parts of the same tumor may be an expression of the effect of the menstrual cycle on the growth of carcinoma in the breast.

#### SUMMARY

A tumor of the breast is described in which two varieties of carcinoma cells are found: (1) cells of the primary growth situated in the ducts; (2) epithelial cells of the lobules, which have become carcinomatous.

The transition of the normal cells of the ductules (and acini) into carcinoma cells is described and figured.

Dr. Margaret Sturgis has given me permission to publish this case. Dr. Stanley P. Reimann has furnished the photomicrographs and Miss Sophy Ksido the extremely accurate drawings reproduced.

# Laboratory Methods and Technical Notes

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## THE PRESUMPTIVE KAHN PROCEDURE IN SYPHILIS BASED ON 15,000 EXAMINATIONS\*

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It is known that the presumptive Kahn procedure is capable of detecting smaller amounts of syphilitic reagin than the regular Kahn test.<sup>1</sup> The degree of the greater sensitiveness of this procedure, however, heretofore has not been determined in a large group of cases. From July, 1928, when the Kahn test was made standard in this laboratory, to March, 1929, data have been collected on the sensitiveness of the two procedures. This report gives the results, based on 15,277 examinations in general hospital cases and in 150 cases in which the patients were being treated for syphilis.

*Relative Sensitiveness of Presumptive and Regular Tests in Hospital Cases in General.*—The Kahn test is performed on the blood of all patients admitted to this hospital. Two methods are employed as a routine in examining each specimen, the regular or conservative method and the more sensitive presumptive procedure. For patients being treated for syphilis, the quantitative Kahn test is also employed.

Table 1 illustrates the increase in sensitiveness of the presumptive procedure over the regular in 15,277 examinations. Of 1,288 serums giving ++++ or +++ reactions with the presumptive procedure, only 878 gave similar reactions with the regular test; of the remaining number, 173 gave ++ or + reactions, 75  $\pm$  reactions and 162 negative reactions. Of 181 serums giving ++ or + reactions with the presumptive procedure, 20 gave ++++ or +++ reactions with the regular test, 5 ++ or + reactions, 8  $\pm$  reactions and 148 negative reactions. Of 197 serums that gave  $\pm$  reactions with the presumptive procedure, 3 gave ++++ or +++, 1 ++ or +, and 193 negative reactions with the regular procedure. The presumptive procedure was negative with 13,611 serums; the regular test gave a strongly positive reaction with 1 of these serums, and was negative with the remaining 13,610 serums.

In considering the totals and the percentages of the various reactions obtained in the 15,277 examinations, I find that of the 1,288 serums that were ++++ or +++ with the presumptive procedure, 902 gave similar reactions with the regular test, so that a 2.5 per cent increase in sensitiveness was shown for the presumptive procedure. Of the ++ or + reactions, a percentage of 1.2 was obtained with both methods. The presumptive procedure gave 197  $\pm$  reactions, or 1.3 per cent, and the regular test 83, or 0.5 per cent.

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\* Submitted for publication, June 6, 1929.

\* From the Serological Laboratory, University Hospital, University of Michigan.

1. Kahn, R. L.: The Kahn Test, A Practical Guide, Baltimore, Williams and Wilkins Company, 1928, p. 141.

*Increase in Sensitiveness of Presumptive over Regular Test in the Case of Patients Being Treated for Syphilis.*—The aforementioned groups representing largely diagnostic cases, it was desired to determine the extent of the increased sensitiveness of the presumptive procedure in a group of cases in which the patients were undergoing antisyphilitic

TABLE 1.—*The Increase in Sensitiveness of the Presumptive Kahn Procedure Over the Regular Test with 15,277 Serums*

The Reactions Obtained With								
Presumptive Procedure				Regular Test				
1,288	++++ or +++*			878	++++ or +++			
				173	++ or +			
				75	±			
				162	0			
181	++ or +			20	++++ or +++			
				5	++ or +			
				8	±			
				148	0			
197	±			3	++++ or +++			
				1	++ or +			
				...	±			
				193	0			
13,611	0			1	++++ or +++			
				...	++ or +			
				...	±			
				13,610	0			
Totals and Percentages								
	++++ or +++	Per Cent	++ or +	Per Cent	±	Per Cent	0	Per Cent
Presumptive procedure.....	1,288	8.4	181	1.2	197	1.3	13,611	89.1
Regular test.....	902	5.9	179	1.2	83	0.5	14,113	92.4

\* ++++ or +++ = strong precipitation; ++ or + = moderate precipitation; ± = weak or borderline precipitation; 0 = no precipitation.

TABLE 2.—*The Increase in Sensitiveness of the Presumptive Kahn Procedure Over the Regular Test with 150 Serums from Patients Being Treated for Syphilis*

The Reactions Obtained With						
Presumptive Procedure			Regular Test			
118	++++ or +++		75	++++ or +++		
			14	++ or +		
			8	±		
			21	0		
10	++ or +		10	0		
21	0		21	0		
Totals and Percentages						
	++++ or +++	Per Cent	++ or +	Per Cent	0	Per Cent
Presumptive procedure....	118	78.7	10	6.7	22	14.6
Regular test.....	75	50.0	14	9.3	53	35.3

therapy. Table 2 summarizes the results of 150 examinations in comparison with the regular test.

It is seen from this table that of 118 serums that gave ++++ or +++ reactions with the presumptive procedure, 75 gave similar reactions with the regular test, 14 ++ or + reactions, 8 ± reactions and 21 negative reactions. Ten serums that gave ++ or + reactions with the presumptive procedure gave negative reactions with the regular

test. Twenty-one that were negative with the presumptive procedure were also negative with the regular test. The presumptive procedure as compared with the regular test showed an increase of 28.7 per cent in +++ or +++ reactions. The latter test showed an increase of 2.6 per cent in ++ and + reactions, as compared with the presumptive procedure. The  $\pm$  reactions are not listed in this comparison because such reactions with the presumptive procedure are reported negative in view of the high sensitiveness of the latter method.

With regard to the specificity of the presumptive procedure, while it is not quite as specific as the regular test, it appears to be practically free from false reactions. During the eight months in which the present data were collected, ten positive reactions in cases which clinicians believed were nonsyphilitic were called to our attention. There may have been still other such reactions of what we have not been informed. However, in consideration of the close contact between the clinical staffs and the laboratories, one cannot doubt that the incidence of false positive reactions in the presumptive procedure is small.

With the increased use of the Kahn test as the standard method in the serologic diagnosis of syphilis, there will undoubtedly follow a wider use of the presumptive procedure as a supplementary method. The main value of the latter lies in the fact that it serves as a technical check on the regular test, two methods being more dependable than one. The increased sensitiveness of the presumptive procedure strengthens the diagnostic value of the doubtful or borderline reactions of the regular test, and also, in giving a positive reaction in the face of a negative reaction with the regular test, serves as a stimulus to clinicians to search for evidence of syphilis.

It is of interest to mention in this connection that at the international conference on the serologic diagnosis of syphilis held under the auspices of the League of Nations Health Committee, it was recommended that two methods be employed in the serologic diagnosis of syphilis.<sup>2</sup> The use of the regular and the presumptive Kahn procedures conforms to this recommendation.

#### SUMMARY

A study was made of the sensitiveness of the presumptive procedure in comparison with the regular Kahn test, based on 15,277 examinations. It was found that in the general run of hospital cases the presumptive procedure was positive in 2.5 per cent more cases than the regular test. In a group of 150 cases in which the patients were being treated for syphilis, this procedure was positive in 26 per cent more cases than the regular test. In view of the fact that the number of false positive reactions obtained with the presumptive procedure is relatively small, the increase in sensitiveness of this procedure over the regular test renders it an important supplementary method in the Kahn reaction.

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2. Report of the Second Laboratory Conference on Sero-Diagnosis of Syphilis, League of Nations, Health Organization, 1928, p. 12.

# General Review

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## THE ASCHOFF NODULE\*

B. J. CLAWSON, M.D.

MINNEAPOLIS

So much diagnostic emphasis has been placed by pathologists and clinicians on the presence or absence of the Aschoff bodies in the myocardium in cases of cardiac failure that it seems important to consider what is meant by Aschoff nodules. The expression "typical Aschoff nodule" is often found, but it has been the experience of workers studying myocarditis that the literature has been somewhat indefinite in stating what a typical Aschoff body is.

In this review, I have tried to correlate the descriptions of the Aschoff bodies (as they occur in man and as they are produced experimentally in animals) as given by the different observers and to compare their observations, with what I have seen in a study of fifty cases of acute rheumatic endocarditis in the necropsy material at the University of Minnesota and in a study of experimental rheumatic nodules. The question may be raised as to whether what is called the Aschoff nodule is a specific anatomic lesion like the tubercle or the gumma, or whether it is a more or less nodular area of proliferative or exudative inflammation.

### RHEUMATIC NODULES AS OBSERVED IN VARIOUS TISSUES IN MAN

Rheumatic inflammation, either in the form of nodules or in that of irregular groups of large cells, has been described as occurring in the subcutaneous tissues, the joints, the tendons, the galea aponeurotica, the diaphragm, the tongue and other muscles, the tonsils, the arteries and the valves, auricles and ventricles of the heart.

*Subcutaneous Rheumatic Nodules.*—The subcutaneous rheumatic nodule is found in the loose connective tissues beneath the skin in many cases of acute rheumatic fever. Apparently, the first written account of these nodules was that given by Hillier<sup>1</sup> in 1868. In 1875, Meynet<sup>2</sup> pointed out that these nodular areas bore a direct relation to rheumatic

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\* Submitted for publication, Nov. 14, 1928.

1. Hillier: Diseases of Children, Philadelphia, 1868; cited by Jacki, E.: Frankfurt Ztschr. f. Path. **22**:82, 1919-1920.

2. Meynet, P.: Rhumatisme articulaire subaigu avec production de tumeurs multiples, Lyon méd. **19**:495, 1875.

fever. According to Angel Money,<sup>3</sup> the nodules are less frequent in the acute cases than in the chronic. Cheadle<sup>4</sup> seldom found them in acute rheumatic fever, except in childhood.

The first microscopic description of the subcutaneous nodule was that given by Hirschsprung<sup>5</sup> in 1881. He observed that it consisted of different modifications of connective tissue cells varying in size and shape. Some of the cells were spindle-shaped and others were irregular. They each contained one or more vesicular nuclei, which were larger than those found in ordinary granulation tissue, and the ground substance between the cells was homogeneous. There was an increase in the number of blood vessels within the inflammatory area, and the nodule resembled the tubercle in structure without having its typical appearance. He considered the nodule to be a localized area of inflammation with a tendency to undergo necrosis. In 1881, Barlow and Warner<sup>6</sup> described the subcutaneous nodule as a reaction similar to that found in the valves in acute rheumatic endocarditis. The same observation was recently made by Swift<sup>7</sup> and by Clawson and Bell.<sup>8</sup>

Cavafy,<sup>9</sup> in 1883, called attention to the presence of proliferative endarteritis in these nodules. The proliferating intima sometimes completely closed the lumina of the vessels.

The subcutaneous nodules were found by Fitcher<sup>10</sup> to consist of fibrous tissues in various stages of development and the cellular element to be made up of small round cells, fibroblasts and polymorphonuclear leukocytes. Giant cells were also present, some of which contained as many as twenty-six nuclei. Nodules of various stages of development were observed in the same individual. Some nodules had become calcified.

In 1912, Frank<sup>11</sup> described the nodules as being divided into central and peripheral portions. The central area was a homogeneous mass

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3. Money, Angel: Surface and Subsurface Nodular Rheumatism, *Lancet* 1:540, 1891.

4. Cheadle, W. M.: Harveian Lectures: On the Various Manifestations of the Rheumatic State in Childhood and Early Life, *Lancet* 1:871, 1889.

5. Hirschsprung: *Jahrb. f. Kinderh.*, 1881; cited by Frank, P.: *Berl. klin. Wchnschr.* 49:1358, 1912.

6. Barlow, T., and Warner, F.: On Subcutaneous Nodules, *Tr. Seventh Internat. Med. Cong. London* 4:116, 1881.

7. Swift, H. F.: Pathogenesis of Rheumatism, *J. Exper. Med.* 39:497, 1924.

8. Clawson, B. J., and Bell, E. T.: Valvular Diseases of the Heart, *Am. J. Path.* 2:193, 1926.

9. Cavafy: Rheumatic Nodules, *Brit. M. J.* 1:622, 1883.

10. Fitcher, T. B.: A Study of Subcutaneous Fibroid Nodules, *Bull. Johns Hopkins Hosp.* 6:133, 1895.

11. Frank, P.: Ueber den Rheumatismus nodosus mit besonderer Berücksichtigung des pathologisch-anatomischen Befundes, *Berl. klin. Wchnschr.* 49:1358, 1912.

that stained intensely red with eosin. On special staining, he decided that this homogeneous material was fibrin. The periphery consisted of proliferating connective tissue, which appeared partly as spindle cells and partly as epithelioid cells. Scattered among the proliferating cells often were numerous leukocytes. A variation in structure was noted in different nodules. This variation Frank considered as due to the nodules being at different stages of development. He thought that the primary reaction in the nodule was an exudation of polymorphonuclear leukocytes, and that this was followed by a wandering in of round cells and by a proliferation of the surrounding connective tissue.

According to Swift,<sup>7</sup> the subcutaneous nodules were made up of a conglomerate number of smaller nodules and appeared similar in structure to the nodules found in the heart and other parts of the body. He observed that the center consisted of necrotic material and a small amount of fibrin.

The nodule that I studied was removed from the subcutaneous tissue of a patient with acute rheumatic fever. On microscopic examination of serial sections of the entire gross nodule, I found it made up of many smaller nodular areas of inflammation. The reaction observed was chiefly proliferative, but in many parts polymorphonuclear leukocytes, lymphocytes and what appeared to be fibrin were noted. The proliferative cells varied in size, in shape and in staining qualities. Some of the nuclei were vesicular and some were hyperchromatic. The cytoplasm also varied in the degree to which it took the basic stains. Many of these cells were multinucleated. Some of the nodular areas showed more or less necrosis in the centers. There was an increase in the number of blood vessels, and proliferative endarteritis was noted in the smaller vessels. Morphologically, the reaction observed in this nodule was similar to that described by Hirschsprung,<sup>5</sup> Fletcher,<sup>10</sup> Frank<sup>11</sup> and others.

Summary: There seems to be a general agreement by observers who have studied the subcutaneous rheumatic nodules that they consist of proliferating connective tissue cells and a cellular exudate of lymphocytes, plasma cells and polymorphonuclear leukocytes in varying numbers; and that in the center of most of the nodules there is a greater or less amount of homogeneous substance consisting of necrotic material and fibrin.

*Rheumatic Nodules in the Galea Aponeurotica.*—The rheumatic nodules in the galea aponeurotica of a child 10 years old were studied by Tilph.<sup>12</sup> On microscopic examination, he found them divided each into a central and a peripheral portion. The center contained a mass

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12. Tilph: Nodi rheumatici galeae aponeuroticae, Verhandl. deutsch. path. Gesellsch. 17:469, 1914.

free from nuclei and composed of a material partly fibrillar and partly serous. In the peripheral part were irregular spindle-shaped, multinucleated cells. The multinucleated cells resembled those found in lymphogranulomas. He concluded that the nodules found in the galea aponeurotica were like those in the subcutaneous tissues described by Frank<sup>11</sup> and those in the myocardium described by Aschoff.<sup>13</sup>

The rheumatic nodules in the galea aponeurotica in the cases of acute rheumatic fever described by Jacki<sup>14</sup> did not differ essentially from those in other parts of the body. As seen microscopically, the structure consisted of a proliferative process with some exudation. Giant cells of the Sternberg type with from two to sixteen nuclei were seen. She thought that, genetically and morphologically, the nodules in the galea aponeurotica were similar to the Aschoff bodies in the heart of the same patient and that the small difference that at times was observed could be accounted for on the basis of the different ground substances in which the nodules developed and the different stages of their development.

*Rheumatic Nodules in the Joints.*—Lesions in the joints with a reaction resembling that found in the nodules in the subcutaneous tissues, in the galea aponeurotica and in the heart were described by Fahr,<sup>15</sup> Swift<sup>7</sup> and Graff.<sup>16</sup> The lesions in the joints examined by Fahr<sup>15</sup> in typical cases of acute rheumatic arthritis did not have the giant cells. He considered the anatomic differences between the inflammation in the joints and the nodules in other parts of the body to be a quantitative one and thought that this quantitative difference might be due to the duration of the action of the virus. He also found that nodules in places other than the heart tended to show a greater degree of necrosis. Swift<sup>17</sup> stated that the variation in other focal lesions from the picture of the Aschoff body in the heart was explained by the difference of the tissues involved and the presence of a superimposed exudative process. Graff<sup>16</sup> was convinced that in the joints and their surrounding tissues the reaction, though less nodular, was as specific as the nodules.

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13. Aschoff, L.: Zur Myocarditisfrage, Verhandl. d. deutsch. path. Gesellsch. 8:46, 1904.

14. Jacki, Elizabeth: Ueber rheumatische Knötchen in der Galea aponeurotica und ihre histologische Uebereinstimmung mit den Aschoffschen Myokardknötchen, Frankfurt. Ztschr. f. Path. 22:82, 1919-1920.

15. Fahr, T.: Beiträge zur Frage der Herze und Gelenkveränderungen bei Gelenkrheumatismus und Scharlach, Virchows Arch. f. path. Anat. 232:134, 1921.

16. Graff, S.: Zur pathologischen Anatomie und Pathogenese des Rheumatismus infectiosus, Deutsche med. Wchnschr. 53:708, 1927; München. med. Wchnschr. 74:473, 1927.

17. Swift, H. F.: Rheumatic Fever, Am. J. M. Sc. 170:631, 1925.



He found in the joints nodular areas that were as characteristic as those found in the subcutaneous tissues or in the heart.

Nodular areas with a proliferative and exudative reaction were found by Graff<sup>16</sup> and others in cases of acute rheumatic fever in the diaphragm, the tongue and other muscles, the tendons, the fasciae and the tonsils. Maclachlan<sup>18</sup> found granuloma-like lesions in the tonsils from rheumatic patients.

*Rheumatic Nodules in the Arteries.*—Portions of the arterial system, according to Klotz,<sup>19</sup> were as frequently attacked in rheumatism as the musculature of the heart. In a series of arteries studied by him in cases of acute rheumatic fever, he found the inflammatory lesions limited to the adventitia and the media. The lesion consisted of an exudate along the smaller nutrient vessels. This exudate was composed chiefly of lymphocytes and plasma cells, but polymorphonuclear leukocytes sometimes were present in large numbers. The exudative reaction was accompanied with a destruction of muscle and elastic connective tissue.

Pappenheimer and von Glahn,<sup>20</sup> in a comparative study of the aorta in seventy-six cases of acute rheumatic fever and seventy-seven cases in which death resulted from nonrheumatic causes, described what they considered a distinctive lesion of the arteries in many of the rheumatic cases. The lesion was a scar in the region of the nutrient vessels in the media, often acellular, but large mononuclear and multinucleated cells were in some cases arranged irregularly or in nodules in the adventitia. This type of lesion was found in only one of the seventy-seven cases of nonrheumatic diseases. In this case, the patient died with pneumococcic meningitis. Aschoff bodies were present in the heart. In a later study of the aorta in a case of acute rheumatic fever, the large multinucleated cells were found in the media, as well as in the adventitia.

The effect of rheumatic infection on the smaller vessels in various parts of the body was also studied by von Glahn and Pappenheimer.<sup>20</sup> In a study of forty-seven cases, they found what they considered to be a specific lesion in ten cases. The endothelium became swollen and basophilic, and sometimes it was raised from its basement membrane

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18. Maclachlan, W. W. G., and Wayne, G. R.: Histopathology of the tonsil in Acute Rheumatic Fever, *Arch. Int. Med.* **1**:506 (Jan.) 1928.

19. Klotz, A.: Rheumatic Fever and the Arteries, *Tr. A. Am. Phys.* **17**:181, 1912; Arterial Lesions Associated with Rheumatic Fever, *J. Path. & Bact.* **18**:259, 1913.

20. Pappenheimer, A. M., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, *J. M. Research* **44**:489, 1924; A Case of Rheumatic Aortitis with Early Lesions in the Media, *Am. J. Path.* **2**:15, 1926; Specific Lesions of the Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* **2**:235, 1926.

by a coagulated exudate. The vessel wall was thickened from a fibrinous exudate. Evidence of necrosis was present in all parts of the wall. Red cells could be seen either immediately beneath the endothelium or in the meshes of the fibrin. Exterior to the necrotic wall there was a cellular exudate, many cells of which were polymorphonuclear leukocytes showing various stages of necrosis. There were also cells with large vesicular nuclei, plasma cells, eosinophils, young connective tissue cells and branching or polygonous mononuclear or multinucleated cells with deeply staining nuclei.

Chiari,<sup>21</sup> studying the vessels in seven cases of acute rheumatic fever, noted diffuse and nodular proliferative inflammation in the adventitia. The nodules showed a cellular reaction not unlike the reaction in the Aschoff nodules.

In a study of the pulmonary artery in twenty-two cases of acute rheumatic carditis, Krugel and Epstein<sup>22</sup> found, in five, active inflammatory changes, consisting, on the one hand, of diffuse cellular infiltration in the media and the subintimal layers of the media, and, on the other hand, of a focal perivascular involvement of the arteries with a cellular reaction comparable to that in the Aschoff nodules in the myocardium.

Summary: The arterial injury described by Klotz,<sup>19</sup> by Pappenheimer and von Glahn,<sup>20</sup> by Chiari<sup>21</sup> and by Krugel and Epstein<sup>22</sup> showed exudative, proliferative and retrogressive processes. The cellular exudative consisted of plasma cells, lymphocytes, eosinophils and polymorphonuclear leukocytes. There was also the fibrinous exudate, as observed in the subcutaneous rheumatic nodules by Frank<sup>11</sup> and Swift.<sup>7</sup> The proliferative reaction was made up of large and irregular mononuclear and multinucleated cells, apparently like the large cells in rheumatic nodular areas of inflammation in other parts of the body. The retrogressive process was made evident by the necrosis. The necrotic process was emphasized by Fraenkel<sup>23</sup> as characteristic of rheumatic inflammatory areas in the heart, and by Frank<sup>11</sup> as characteristic of subcutaneous rheumatic nodules. The reaction in the arteries in cases of acute rheumatic fever appeared to be the same as that found in other foci of rheumatic inflammation.

*Rheumatic Nodules in the Heart.*—Greater consideration has been given to rheumatic nodules in the heart than to those in any other part

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21. Chiari, H.: Ueber Veränderungen in der Adventitia der Aorta und ihrer Hauptäste im Gefolge von Rheumatismus, Beitr. z. path. Anat. u. z. allg. Path. 80:337, 1928.

22. Krugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, Arch. Path. 6:247 (Aug.) 1928

23. Fraenkel, E.: Ueber Myocarditis rheumatica, Beitr. z. path. Anat. u. z. allg. Path. 52:597, 1912.

of the body. Areas of rheumatic inflammation in the heart are found in the valves, auricles and ventricles.

Valves: Barlow and Warner,<sup>6</sup> in 1882, observed a reaction in the valves in cases of acute rheumatic endocarditis similar to that in rheumatic subcutaneous nodules. The inflammatory process in the valves was considered by Swift<sup>7</sup> to be essentially the same as that found in the nodules in the myocardium. He found typical submiliary nodules in the valves. A microscopic study of the valves in cases of acute rheumatic endocarditis from the material available at the University of Minnesota repeatedly showed nodular inflammatory areas with large irregular mononuclear and multinucleated cells. Such typical cellular inflammatory areas were also commonly seen in the valves in cases of subacute bacterial endocarditis.

Auricles: In many cases of acute rheumatic endocarditis, MacCallum<sup>24</sup> noticed a marked thickening of the wall of the left auricle, which he decided was produced mostly by a new growth and to a less extent by a deposit of fibrin on the surface. The layers of the auricles were spread apart by a fluid and by a great infiltration of wandering cells, most of which were mononuclear, but many of which were polymorphonuclear leukocytes and lymphocytes. Most striking were the Aschoff bodies composed of the characteristic large cells. All modifications of these large cells leading to the giant cells were observed. The large cells were forced into rows by the arrangement of the elastic lamellae, so that the Aschoff bodies had a banded appearance.

Of the thirty-one cases of rheumatic endocarditis examined by von Glahn,<sup>25</sup> nine showed a rheumatic inflammatory involvement of the auricles and a gross thickening of the endocardium. On microscopic examination, he observed an exudate consisting of an accumulation of lymphocytes, many polymorphonuclear leukocytes and a few eosinophils. There were the typical large cells arranged radially around a hyalinized center or in palisades. The radial appearance of the nodule he interpreted as probably being a transverse section of one of the elongated palisades. In some sections, he found cells with indistinct outlines, having compressed, distorted, curved and elongated nuclei. With these indistinct cells there were many polymorphonuclear leukocytes, a few eosinophils, small round cells and an occasional plasma cell. In some cases, the polymorphonuclear leukocytes predominated and tended to obscure all the other elements. Von Glahn concluded that the masses of distorted cells and polymorphonuclear leukocytes constituted a feature as prominent and distinctive as the Aschoff bodies.

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24. MacCallum, W. G.: Rheumatic Lesions of the Left Auricle of the Heart, *Bull. Johns Hopkins Hosp.* **35**:329, 1924.

25. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, *Am. J. Path.* **2**:2, 1926.

In my material, microscopic evidence of infection in the auricles was found almost constantly. The reaction was chiefly proliferative and, in some cases, arranged in nodular forms, but there was a great tendency for the proliferation, as well as the exudation, to have a diffuse arrangement. The type of cells did not differ from that found in the nodules in the subcutaneous tissues, ventricles, etc.

Ventricles: The nodular areas of inflammation have been studied more extensively in the ventricles, especially in the left ventricle, than in any other part of the body. These are the nodules that are regularly called the Aschoff bodies. MacCallum<sup>24</sup> found them located chiefly in the left ventricle near its base posteriorly. According to Thalhimer and Rothschild,<sup>26</sup> they were most frequent in the left ventricle. Coombs<sup>27</sup> noted that they were likely to be found in the subendothelial and subepicardial tissues. It has been my experience that the nodules were as frequent in the apex of the left ventricle as in any other part and that they were less frequent in the right ventricle.

The nodules, according to Aschoff,<sup>13</sup> regularly lie in the immediate vicinity of the small or medium size blood vessels, and often show an immediate involvement of the adventitia or at times the other layers of the vessels. He observed that the cells might extend out from the nodule between the muscle fibers, or the nodules might occur between the muscle fibers without any relation to vessels of noticeable size. Aschoff's observations in regard to the location of these nodules were confirmed by Geipel,<sup>28</sup> Coombs,<sup>27</sup> Bracht and Wächter,<sup>29</sup> Takayasu,<sup>30</sup> Fraenkel,<sup>23</sup> Huzella,<sup>31</sup> Thalhimer and Rothschild,<sup>26</sup> Swift<sup>7</sup> and others. Huzella<sup>31</sup> suggested that the immediate proximity of the nodules to the blood vessels resulted from the resistance that the vessels offered to the extension of the nodule. Swift<sup>7</sup> noted that frequently the inflammatory reaction might extend entirely around the vessel or even push into the lumen. On studying serial sections, I commonly found the nodule

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26. Thalhimer, W., and Rothschild, M. A.: On the Significance of the Sub-miliary Myocardial Nodules of Aschoff in Rheumatic Fever, *J. Exper. Med.* **19**: 417, 1914.

27. Coombs, C.: Myocardial Lesions of the Rheumatic Infection, *Brit. M. J.* **2**:1513, 1907.

28. Geipel, P.: Untersuchungen über rheumatische Myokarditis, *Deutsches Arch. f. klin. Med.* **85**:75, 1905-1906.

29. Bracht, E., and Wächter, A.: Beitrag zur Aetiologie und pathologischen Anatomie der Myocarditis rheumatica, *Deutsches Arch. f. klin. Med.* **96**:493, 1909.

30. Takayasu, R.: Zur Kenntnis der Sogenannten Endarteritis infectiosa und der Knötchenbildung bei rheumatischer maligner Endokarditis, *Deutsches Arch. f. klin. Med.* **95**:270, 1909.

31. Huzella, T.: Ueber rheumatische Myokarditis, *Virchows Arch. f. path. Anat.* **213**:389, 1913; Ueber histologische Befunde bei Rheumatismus und Chorea, *Verhandl. d. deutsch. path. Gesellsch.* **17**:470, 1914.

surrounding the vessels, especially the smaller ones. In reality, such a condition is an arteritis and corresponds closely to the arteritis observed in the subcutaneous nodules by Cavafy<sup>9</sup> and the arteritis referred to by Klotz<sup>19</sup> and by Pappenheimer and von Glahn.<sup>20</sup> The frequency of this perivascular arrangement of the rheumatic inflammation suggests that the early nodule begins in the small vessels even when the nodule is found in the adventitia of the larger vessels.

The nodule, as first described by Aschoff,<sup>13</sup> was roset or fan-shaped. There was a tendency for it to become elongated and irregular and to extend out between the muscle fibers. As seen by Geipel,<sup>28</sup> the nodules were round, oval or fusiform bodies. In cross-section, they were round or oval. In some of our cases, the nodules confined themselves mainly to the adventitia of the vessels and took on a roset or spindle shape, while in other cases the nodules occurred chiefly in the interstitial tissues away from the larger blood vessels and were fusiform in outline or extended extensively and irregularly throughout interstitial areas of the heart. The inflammation, instead of being arranged in a nodular form, sometimes was so extensive as to appear as a diffuse interstitial myocarditis. This condition was noted by Wätjen<sup>32</sup> and Freund.<sup>33</sup> A diffuse myocarditis was also present in one of the cases described by Geipel.<sup>28</sup>

In my material, marked variations were noted in the size of the nodules. They sometimes consisted of but a few cells near or surrounding blood vessels, and sometimes they were large enough to extend entirely across a section more than a centimeter in width. This I have found in different cases. Nodules were reported by Geipel<sup>28</sup> 1 mm. in length. Fahr<sup>15</sup> described them as 0.8 mm. in diameter. MacCallum<sup>24</sup> was able to see them with the naked eye. It is evident that the nodules are not of uniform size and that they may vary from a few cells to rosets, fusiform bodies or a diffuse myocarditis.

I found that the number of nodules varied greatly in different hearts and in different parts of the same heart. In some cases, several sections had to be examined to find a single nodule, while, in others, the nodules were so numerous that as many as ten could be seen in a single low power microscopic field.

According to the literature, there is a decided variation in the microscopic structure of the nodules. The two chief zones described by Hirschsprung<sup>5</sup> and Frank<sup>11</sup> as occurring in the subcutaneous nodules,

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32. Wätjen: Ein besonderer Fall rheumatischer Myokarditis, *Verhandl. d. deutsch. path. Gesellsch.* **18**:223, 1921.

33. Freund, G.: Zur Kenntnis der acuten diffusen Myocarditis, *Berl. klin. Wchnschr.* **35**:1077, 1898.

are described as occurring also in the nodules in the heart, i.e., the central and the peripheral zones. The peripheral zone consists in general of a proliferative structure, surrounding the central zone, and an exudative structure, which, as a rule, lies external to the proliferative structure, but the proliferative and exudative cells may be intermixed. As seen by Aschoff,<sup>13</sup> the center of the nodule consisted of a poorly staining or stainless substance that appeared to be a necrotic mass of fused protoplasm. The central necrotic area appeared to him to arise later in the development of the nodule. Geipel<sup>28</sup> studied this necrotic center extensively. He described the hyalinized center as being present in most nodules and noticed that this necrotic material might contract and form a cavity in the center. Thalheimer and Rothschild<sup>26</sup> reported strands in the central mass, which they thought might be fibrin. Contrary to Aschoff, Geipel<sup>28</sup> and Thorel<sup>34</sup> considered the center of the nodule as the earliest stage in its development. According to Pappenheimer and von Glahn,<sup>20</sup> the large cells of the nodules occurred as a result of an injury to primary connective tissue. This is in agreement with Maximow's<sup>35</sup> statement that the polyblasts could assume the forms of giant cells in the presence of foreign bodies. Takayasu,<sup>30</sup> in his study of the nodules, was not able to find the hyalinized necrotic center. The center was described by Coombs<sup>27</sup> as consisting of closely packed large cells. Swift<sup>17</sup> was of the opinion that necrosis was present in the centers of most nodules. In my material, studied in serial sections, many nodules showed the necrotic center, while others showed only the proliferative and exudative reactions.

On the basis of the cellular content, two types of nodules are described: those consisting primarily of large mononuclear or multinucleated cells, and those consisting, for the most part, of large and small lymphocytes, plasma cells, eosinophils and polymorphonuclear leukocytes. Various stages between these two extremes are seen. Occasionally, nodules contain chiefly polymorphonuclear leukocytes and become abscesses. In the description of the nodule, Aschoff<sup>13</sup> referred to the large cell type, and in the illustration in his textbook on pathology he<sup>36</sup> showed the lymphocytic type. He described the cellular zone of the nodule as consisting of large cells each with one or more nuclei, which might be notched or polymorphous. The multinucleated cells he called giant cells, but considered them different from the giant cells found in tuberculosis. They had the appearance of the multinucleated cells found in Hodgkin's disease or of the cells in a sarcoma.

34. Thorel, C.: *Pathologie der Kreislauforgane*, *Ergebn. d. allg. Path. u. path. Anat.* **14**:315, 1910.

35. Maximow, A.: *Mesenchymal Reactions*, *Arch. Path.* **4**:557 (Oct.) 1927.

36. Aschoff, L.: *Pathologische Anatomie* **2**:34, 1921.

He stated that the nodules were not composed entirely of the large cells, but had large and small lymphocytes in the periphery between the large cells, or, in some cases, forming an irregular zone of extension out into the connective tissue septums. In these cellular extensions of the nodules, separate large cells could be seen which showed transition forms of the various stages of the large cells.

Both types of nodules were described by Fraenkel.<sup>23</sup> His illustrations showed the nodules to be made up of fusiform bodies consisting almost entirely of more or less spindle-shaped large cells. He described the cellular content of the periphery as being essentially the same as that seen by Aschoff. Geipel,<sup>25</sup> however, laid more stress on the presence of polymorphonuclear leukocytes. He found, in some cases, a rich mixture of these leukocytes. In one of his seven cases there were abscesses as well as Aschoff nodules scattered through the heart. He considered these due to a secondary invasion of staphylococci. In one case, Thalheimer and Rothschild<sup>26</sup> found, associated with the Aschoff bodies in the myocardium, other nodular areas of inflammation identical with those produced experimentally by Bracht and Wächter.<sup>29</sup> This association was interpreted as a rheumatic process with an added bacterial involvement. Such nodules are essentially abscesses. In two of my cases, I found both Aschoff bodies and abscesses in the myocardium. The histories of these two cases follow:

CASE 1.—A white boy, aged 9, complained of joint pains, headache, vomiting and difficulty in breathing. His right ankle was swollen and tender for three or four days. After three weeks, he complained of pain in the epigastrium and then in all the joints of the body. Four weeks prior to his admission to the hospital, he was compelled to sleep sitting up because of difficulty in breathing.

Physical examination showed the tonsils enlarged and a definite pericardial rub. The blood showed 5,760,000 red cells per cubic millimeter and a hemoglobin content of 61 per cent. The white cell count was 16,900. The temperature ranged from 99 to 100 F.

The postmortem examination revealed marked edema extending from a point about the level of the umbilicus downward to the ankles. The face showed many purplish areas having the gross appearance of petechiae, particularly around the eyes. Several of these areas were present on the conjunctiva of the lower lid. The two layers of the pericardium were firmly adherent to each other by fibrinous adhesions that were beginning to organize. The heart weighed 165 Gm. It was dilated in both chambers. A large mural thrombus was present in the tip of the right ventricle and also in the right auricular appendage. The mitral leaflets showed numerous pinhead size pearly white nodules along the entire line of contact with the valves. In places, the nodules were present on the chordae tendineae. The aortic cusps had similar vegetations on the ventricular surfaces. Multiple small infarcts were found in the spleen, lungs and both kidneys.

Microscopically, the structure of the nodules and the valves was characteristic of rheumatic valvulitis. On the free edges of the small vegetations, many gram-positive cocci were present, as seen in smears taken from the valve and also in microscopic sections stained by the Gram-Weigert method. On microscopic study

of the myocardium, Aschoff nodules were found, as well as typical abscesses, both often in the same microscopic field. In the abscesses, gram-positive cocci were seen. On the epicardium, cocci in large numbers were present as could be seen in sections stained for bacteria.

CASE 2.—A white man, aged 34, three weeks prior to his death became ill with an acute infection of the maxillary sinus. Ten days before death, he developed a multiple arthritis with a temperature of from 101 to 103 F. He became irrational and restless and died in coma.

The necropsy showed, scattered over the trunk and the neck, numerous small vesicular and hemorrhagic areas. Subpleural petechial hemorrhages were seen over the surfaces of both lungs. The pericardial cavity contained a small amount of thin, cloudy fluid. Scattered over the heart were numerous subepicardial petechial hemorrhages. On the mitral valve along the line of closure were numerous small smooth nodules that, on microscopic examination, showed a typical rheumatic valvulitis. The heart muscle contained both Aschoff nodules and abscesses. In the abscesses, gram-positive cocci were seen. *Streptococcus viridans* in pure culture was grown from the spleen.

The polymorphonuclear leukocytes in the nodules were noted by Bracht and Wächter,<sup>29</sup> who stated that many of the nodules resembled mildly enlarging abscesses. They believed that, in the early stage, the nodules were made up primarily of polymorphonuclear leukocytes and lymphocytes, which later disappeared and were replaced by the proliferative large cells. This conception agrees with what has been found in nodules produced experimentally in animals. Fraenkel<sup>23</sup> also stressed the fact that the large cells were generally mixed with polymorphonuclear leukocytes and lymphocytes and that in many cases the lymphocytic content of the nodule markedly predominated. Illustrations of both types of nodules were given by MacCallum.<sup>37</sup>

It is apparent that there are many variations in the structure of the nodules in the heart, as well as in those in the subcutaneous tissues. These variations might be explained, as suggested by Frank<sup>11</sup> and Fahr,<sup>15</sup> as representing various stages in the development of the nodule. The part of the nodule sectioned, whether periphery or center, also has to be taken into account in interpreting the nodular structure. It would seem that Aschoff's conception that the hyalinized necrotic center occurred in the later stage in the development of the nodule is the more likely, for otherwise this hyalinized center should be found in all nodules. This is found not to be the case when nodules are examined in serial sections.

From the various descriptions, it appears that the periphery of the nodule, in most cases, consists of proliferative large cells, but in many cases, the lymphocytic element predominates. The polymorphonuclear leukocytic content appears to vary. From a study of the literature and

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37. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1920, pp. 468 and 572.



my fifty cases, one may come to the conclusion that the nodule may represent any stage from the active acute exudative stage (almost an abscess), which is less common, through the exudative lymphocytic stage to the almost pure proliferative condition, in which the large mononuclear and multinucleated cells are chiefly found.

The origin of the cells in the nodule, especially the large mononuclear and multinucleated cells, is of much interest. The large cells have come to be called the Aschoff cells regardless of whether they are found in the nodules or not. These cells, according to Aschoff,<sup>13</sup> had been described by Hayem and Romberg. Aschoff,<sup>13</sup> in 1904, described the cells as arising from the "lymphocytoiden element" that occurred normally in the tissues surrounding blood vessels and in all inflammatory conditions. In a later discussion, he<sup>36</sup> considered these large cells to be of connective tissue origin.

Geipel<sup>28</sup> was definite in his opinion in regard to the origin of these large proliferating cells. He found that the connective tissue cells became swollen and that the nuclei as well as the protoplasm divided. The cells became multinucleated apparently by cell division or by fusion and formed giant cells, which surrounded the old existing connective tissue cells.

The appearance of these large cells suggested to Coombs<sup>27</sup> that they were the product of connective tissue proliferation in response to an irritant. In the opinion of Huzella,<sup>31</sup> they were composed of swollen connective tissue cells, which finally underwent degeneration. Sacks<sup>38</sup> apparently was convinced that they originated from the histiocytes, although he expressed some doubt concerning the source of these cells. The histiocytes, as shown by Maximow,<sup>35</sup> might originate either from the loose connective tissue cells at the point of injury or from any of the nongranular cells in the blood.

The so-called Aschoff cells described by these authors appear to be the cells called polyblasts by Maximow,<sup>35</sup> who described them as small cells that looked like lymphocytes or as medium size cells that remind one of monocytes or as huge cell bodies with abundant cytoplasm. These polyblasts, he stated, could transform themselves into epithelioid cells of extremely varying aspect and in the presence of foreign bodies could fuse and produce multinucleated giant cells. The large cells in rheumatic infection were called wandering cells by MacCallum and by Thalhimer and Rothschild.

The possibility that these large cells in rheumatic inflammation arose from muscle was suggested by Saigo,<sup>39</sup> Huzella<sup>31</sup> and Whitman and

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38. Sacks, B.: The Pathology of Rheumatic Fever, *Am. Heart J.* **1**:750, 1925-1926.

39. Saigo, Y.: Dei Purkinjeschen Muskelfasern bei Erkrankung des Myocards, *Beitr. z. path. Anat. u. allg. Path.* **44**:296, 1908.

Eastlake.<sup>40</sup> In the periphery of the cells in a case reported by Whitman and Eastlake, striae were found that suggested that at least some of the Aschoff cells were derived from muscle fibers. The pathogenesis of these cells was considered a proliferation of the nuclei following degeneration, which might be brought about by the presence of minute infarcts. MacCallum<sup>24</sup> showed definitely that, in the auricles, these cells were not of muscular origin, since they could be found in regions in which muscle did not exist. These are evidently the cells that were called macrophages by Metchnikoff, clasmatoocytes by Ranvier, resting wandering cells by Maximow<sup>35</sup> and adventitial cells by Marchand. All these might be included under the term histiocyte. This is the term used by Sacks<sup>38</sup> for the primitive cell from which the Aschoff cell develops. In the opinion of Swift,<sup>7</sup> the large cells arose from the endothelium, but Maximow<sup>35</sup> was not able to demonstrate the development of polyblasts from the endothelium of common blood vessels. It seems evident that, in the rheumatic inflammation, the polyblasts in their various forms are chiefly concerned.

#### SPECIFICITY OF RHEUMATIC NODULES

The rheumatic nodule in its various forms is generally believed to be a specific type of inflammatory reaction. While Aschoff<sup>13</sup> was not the first to describe the characteristic cell reaction in rheumatic inflammation, he first emphasized the idea that the nodules might represent a specific type of reaction to the rheumatic virus. He studied the nodules in two cases of myocarditis associated with acute rheumatic fever and concluded that such nodules were specific for rheumatic infection. Geipel,<sup>28</sup> Coombs,<sup>27</sup> Fraenkel,<sup>23</sup> Bracht and Wächter,<sup>29</sup> Huzella,<sup>31</sup> Talhimer and Rothschild<sup>26</sup> and others also decided that the nodules were specific for the rheumatic virus. While Fraenkel<sup>23</sup> considered the nodules a specific reaction to the rheumatic infection, he insisted that they were not found in the myocardium in all cases of rheumatic endocarditis. Mönkeberg<sup>41</sup> was not convinced concerning the specific rheumatic etiology of the nodules.

Among the different reasons for the belief in the anatomic specificity of the nodules are the following: The nodules have distinctive histologic characteristics. They are frequently encountered in acute rheumatism; they are infrequently found in other kinds of acute infectious diseases. Nodules similar morphologically and in staining characteristics have not been produced experimentally.

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40. Whitman, R. C., and Eastlake, A. C.: Myocarditis: Histogenic Study of the Type Cells of the Aschoff Body, *Arch. Int. Med.* **26**:601 (Nov.) 1920.

41. Mönkeberg, J. G.: Herzschwache und plötzlicher Herztod als Folge von Erkrankungen des Atrioventrikularsystems, *Ergebn. d. allg. Path. u. path. Anat.* **14**:596, 1910.

*Distinctive Pathologic Characteristics.*—The reaction found in the rheumatic inflammatory lesion is exhibited mainly in the activity of the histiocytes. The same reaction may be seen in different degrees in any subacute or chronic inflammation. The rheumatic inflammation is not a constant type of reaction. There may be nodular and diffuse areas of proliferative inflammation or there may be varying degrees of exudation. The lesion may closely simulate the abscess. Necrosis may be present or absent. The character of the reaction varies in different parts of the body. The reaction may be perivascular, it may involve all the layers of the vessels or it may occur without conspicuous relationship to easily seen vessels. It appears that the inflammation in rheumatism is not necessarily distinctive and that the specificity of the histologic characteristics cannot be considered entirely confirmed.

*The Frequency of the Aschoff Nodule in Acute Rheumatic Endocarditis.*—It is interesting to consider the constancy with which the Aschoff nodules are found in the heart in cases of endocarditis with acute rheumatic fever. Aschoff<sup>13</sup> found them in both of the two cases of rheumatic endocarditis that he studied. The nodules were present in Geipel's<sup>28</sup> seven cases. In the seven cases studied by Coombs<sup>27</sup> the nodules were present. In seventeen of the twenty cases of rheumatic endocarditis studied microscopically by Fraenkel,<sup>23</sup> nodules were present. Bracht and Wächter<sup>29</sup> observed them in three cases. Takayasu<sup>30</sup> saw Aschoff nodules in a case of what he called malignant rheumatic endocarditis. Huzella<sup>31</sup> studied the myocardium in seven cases of acute rheumatic endocarditis, in all of which the Aschoff nodules were present. He also found them in the heart in two cases of chorea. In one case of rheumatic endocarditis and in two cases of chorea, Douglass<sup>12</sup> found nodules in the heart, which he considered the same as those described by Aschoff and Coombs. Thalheimer and Rothschild<sup>26</sup> examined the myocardium in three cases of acute rheumatic endocarditis and in three cases of chorea and found nodules in all. Tilph<sup>12</sup> found the nodules in one case. Whitman and Eastlake<sup>40</sup> also observed nodules in one case. To 1914, the aforementioned authors examined microscopically the myocardium in sixty cases of acute rheumatism or chorea and on this study based their belief in the specificity of the cellular reaction of the nodules; for, in this series of sixty cases, rheumatic nodules were found in the myocardium in fifty-seven cases (95 per cent).

Since 1914, larger series have been studied with a lower incidence of the nodules. In a study of the heart in fifty-six cases of acute rheumatic endocarditis, Libman<sup>43</sup> noted nodules in eighteen cases (32

42. Douglass, M.: Rheumatic Nodules in the Myocardium, *J. Path. & Bact.* **18**:119, 1913.

43. Libman, E.: Characterization of Various Forms of Endocarditis, *J. A. M. A.* **80**:813 (March 24) 1923.

per cent). Thayer<sup>44</sup> examined twenty-four hearts. The nodules were present in twenty-one (87.5 per cent). In my series of fifty cases, the nodules were observed in thirty-one (61 per cent). These reports altogether represent 190 cases either of acute rheumatism or of chorea in which search was made for the Aschoff nodules in the myocardium. The nodules were present in 128 (67 per cent). The fact that the Aschoff bodies were absent in such a high percentage of cases of rheumatic endocarditis coming to necropsy again suggests that what is called the Aschoff body in the heart may not necessarily be a specific lesion produced by a specific virus.

*Aschoff Bodies in the Myocardium in Nonrheumatic Infectious Diseases.*—In cases of typhoid fever, Romberg<sup>45</sup> observed the large type of cell in the interstitial tissues around the blood vessels in the heart. These cells appeared in all respects like those found in cases of acute rheumatic endocarditis by Aschoff and others, but the cells did not appear in nodules. In discussing Coomb's<sup>27</sup> paper on rheumatic myocarditis, Beattie<sup>46</sup> stated that the large cells could be found in nonrheumatic inflammations.

Fahr<sup>15</sup> reported finding proliferative nodular areas in the myocardium in cases of scarlet fever. These nodules had the characteristic location of the Aschoff bodies and the cellular reaction was typical in all respects, except that giant cells were absent. The difference between these nodules and those in acute rheumatic fever seemed to Fahr to be quantitative and to be accounted for by the shorter duration of the process in cases of scarlet fever. Schmorl<sup>47</sup> also found typical rheumatic nodules in the myocardium in a case of scarlet fever. In four of seven cases of scarlet fever, I found nodular areas of proliferation, simulating rheumatic nodules.

In a case associated with pneumonia and possibly produced by the pneumococcus, Pappenheimer and von Glahn<sup>20</sup> found the Aschoff nodules in the myocardium.

The reaction to the syphilitic virus is so similar to rheumatic inflammation that in many cases it is difficult to distinguish between them without the demonstration of the spirochetes in the lesions. In a thorough examination of the myocardium about the aortic ring in fifty cases of syphilitic aortitis, nodular proliferative areas comparable to Aschoff bodies were seen in eight (16 per cent). In some organs with tuberculous infection, the reaction is chiefly proliferative in character.

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44. Thayer, N. S.: Notes on Acute Rheumatic Diseases of the Heart, Bull. Johns Hopkins Hosp. **36**:99, 1925.

45. Romberg, E.: Ueber die Erkrankungen des Herzmuskels bei Typhus abdominalis, Scharlach und Diphtheria, Deutsches Arch. f. klin. Med. **48**:369, 1891.

46. Beattie, J. M.: Discussion of Coomb's paper (footnote 27).

47. Schmorl: Discussion of Huzella's paper (footnote 31).

The proliferative inflammation in the valves in cases of subacute bacterial endocarditis is like that found in the valves in acute rheumatic endocarditis, and the frequency of this similarity seems to be too constant for this inflammation to be considered a separate and distinct associated rheumatic inflammation. Typical nodular areas with giant cells are not infrequently seen in the valves in subacute bacterial endocarditis. Aschoff nodules, when carefully sought, are commonly found in the myocardium in subacute bacterial endocarditis. In twenty-seven (45 per cent) of sixty cases of subacute bacterial endocarditis. Aschoff nodules were found in varying numbers. Many of these were located in partially healed scars. Aschoff nodules or irregular proliferative inflammation or both were noted in 60 per cent of these sixty cases. Various combinations of exudation and proliferation were seen. It was difficult to determine whether some of these areas were abscesses or Aschoff nodules. In some cases, streptococci were found phagocytosed in the large macrophages. As in the valves, this frequency of the presence of the Aschoff bodies and diffuse proliferative inflammation is apparently too great for it to be considered a separate rheumatic infection associated with subacute bacterial endocarditis.

In a case of endocarditis that was shown, by careful checking, to have been produced by the meningococcus, Roads<sup>48</sup> found nodular proliferative areas in the myocardium.

The reaction noted in acute interstitial pneumonia is a proliferative one and, while not in the form of nodules, the cellular reaction resembles that found in the myocardium in acute rheumatic endocarditis. In the inflammation in erysipelas, the cellular reaction consists almost entirely of macrophages. It is worthy of note that the chief cellular reaction to the streptococci is proliferative.

Nodular areas of proliferative inflammation comparable to Aschoff bodies apparently may occur in the myocardium in nonrheumatic infectious diseases, but it is evident that these nodules, except in subacute bacterial endocarditis, are not found nearly as frequently as they are in acute rheumatic fever.

#### EXPERIMENTAL RHEUMATIC NODULES

In 1909, Coombs, Miller and Kettle<sup>49</sup> injected into rabbits intravenously streptococci recovered from the blood of patients with rheumatic infection and produced arthritis, carditis and other lesions. Many of the lesions in the heart were nodular in arrangement and had a

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48. Roads, C. P.: Vegetative Endocarditis Due to the Meningococcus, *Am. J. Path.* **3**:623, 1927.

49. Coombs, C.; Miller, R., and Kettle, E. H.: The Histology of Experimental Rheumatism, *Lancet* **2**:1209, 1912.

reaction that was chiefly proliferative. Large cells were found in the nodules, which corresponded morphologically with those found in rheumatic inflammation in man. They decided that the differences existing between the experimental nodular infection and the infection in man could be accounted for by a difference in the mode of entry of the infectious agent in the two conditions.

Bracht and Wächter<sup>29</sup> injected streptococci into two animals and found lesions in the myocardium consisting of muscle destruction with necrosis and exudation. They also noted some diffuse proliferation. The necrotic areas with polymorphonuclear leukocytic exudation are called Bracht-Wächter bodies. Such bodies are not infrequently found in cases of subacute bacterial endocarditis.

By injecting streptococci into rabbits Thalheimer and Rothschild<sup>50</sup> also produced experimental lesions in the myocardium, which corresponded in character to those of Bracht and Wächter. Thalheimer and Rothschild stated that the organisms were not found in the lesions and suggested that the injury and reaction were produced by toxins and not by the bacteria themselves. They considered the lesions to be different from the Aschoff nodules and thought that the only similarity was the occurrence of the lesions in nodules.

Lesions in the interstitial tissues of the heart were produced by Jackson<sup>51</sup> by injecting streptococci into rabbits. These nodular lesions were composed chiefly of large irregular mononuclear and multinucleated cells, which were not different from those found in the heart in cases of rheumatic infection.

By injecting streptococci into the left ventricular cavity of rabbits, I<sup>52</sup> was able to produce nodular proliferative lesions in the myocardium in a high percentage of cases. Microscopically, these lesions showed many multinucleated cells, the cytoplasm of which stained red with methyl-green-pyronin.

In the myocardium of some of the rabbits into which streptococci had been injected, Belk, Jodzis and Fendrick<sup>53</sup> found nodular lesions that they considered similar to the lesions found in the heart in cases of acute rheumatic endocarditis.

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50. Thalheimer, W., and Rothschild, M. A.: Experimental Focalized Myocardial Lesions Produced by *Streptococcus Mitis*, *J. Exper. Med.* **19**:429, 1914.

51. Jackson, L.: Experimental "Rheumatic Myocarditis," *J. Infec. Dis.* **11**: 243, 1912.

52. Clawson, B. J.: Experimental Rheumatoid Myocarditis, *Arch. Path.* **2**:799 (Dec.) 1926.

53. Belk, W. P.; Jodzis, F. J., and Fendrick, E.: Lesions of Rheumatic Fever Compared with Lesions Produced by *Streptococcus Cardio-Arthritis*, *Arch. Path.* **6**:812 (Nov.) 1928.

Areas of proliferative inflammation, mostly perivascular, were observed by Small<sup>54</sup> in a papule developing at the site of an intradermal injection of a streptococcic vaccine

In a relatively high percentage of rabbits into which had been injected intradermally and subcutaneously strains of streptococci, I<sup>55</sup> was able to produce small nodular proliferative lesions that were, in most cases, entirely similar, in the character of the cellular reaction, to the subcutaneous nodules found in rheumatic inflammation in man.

It is evident that lesions closely simulating those found in the heart and subcutaneous tissues in cases of rheumatic inflammation in man can be produced experimentally in rabbits by the injection of streptococci.

#### COMMENT

The rheumatic nodule is usually a fairly well localized area of inflammation, which has a more or less general distribution, but which is particularly prominent in the heart and subcutaneous tissues. It is not infrequently found in the joints, tendons, galea aponeurotica, diaphragm, tongue and other muscles, arteries, tonsils, etc. In the heart the most common location is the left ventricle, especially at its base and apex; but the right ventricle and auricles may also be involved. The reaction in the valves is similar to the reaction in the ventricles, but tends to be more diffuse.

The shape of the rheumatic nodule shows a great variation. There may be a few cells partially or completely surrounding the small blood vessels. The nodule may take the form of a roset or become more or less fan-shaped or fusiform. It may extend out irregularly into the interstitial tissues between muscle fibers and become greatly elongated, or, at times, the inflammation may be so extensive as to form a diffuse myocarditis. The tendency to form well defined nodules is greatest in the heart and subcutaneous tissues, but even in these locations diffuse and irregular involvement is not infrequent.

There is no regularity of size. The nodule may be composed of a few cells or it may be large enough to be seen with the naked eye. The number of nodules also varies from only one in many sections to so many as almost to replace other structures entirely.

Frequently, but not always, the nodule is made up of two zones, i.e., a central area and a peripheral area. The central zone is composed mostly of necrotic material intermixed with what appears to be fibrin. This central necrotic area is not present in all nodules, as may be ascertained by a study of nodules in serial sections. This suggests that the

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54. Small, J. C.: Rheumatic Fever, *Am. J. M. Sc.* **175**:650, 1928.

55. Clawson, B. J.: Experimental Subcutaneous Rheumatic Nodules, *Am. J. Path.* **4**:565, 1928.

central necrosis occurs as a later development in the pathogenesis of the nodule. The peripheral zone and the nodules without necrotic centers are composed, for the most part, of large, irregular or small cells containing, one or more vesicular nuclei. The cytoplasm of these cells tends to be basophilic. The cells are commonly called the Aschoff cells. Mixed in with the so-called Aschoff cells may generally be found lymphocytes, plasma cells, eosinophils and from a few to many polymorphonuclear leukocytes. The polymorphonuclear leukocytes may be so numerous as to cause the nodule to simulate closely an abscess and, in some cases, there are typical abscesses in the same myocardium with the Aschoff bodies. There appear to be three extremes in the structure of the nodule: the proliferative nodule, composed chiefly of large, irregular, vesicular, mononuclear and multinucleated cells; the lymphocytic nodule, made up mostly of lymphocytes, and the polymorphonuclear leukocytic nodule, or abscess. In frequency, these seem to occur in the order given. All intermediate stages between these extremes are commonly seen. This cellular reaction occurring in the nodules appears to be the same as that seen in the joints and other parts of the body. Necrosis is more common in the nodule than in the diffuse inflammation. The greater tendency for the inflammation in the heart and the subcutaneous tissues to occur as nodules may possibly be accounted for by the structure of the ground substance in which the nodules occur.

Two theories have been given concerning the origin of the large, irregular, vesicular, mononuclear and multinucleated so-called Aschoff cells. A myogenic origin has been suggested. This theory seems to have little foundation. The second theory is that the Aschoff cells arise from existing connective tissue cells or the histiocytes, whatever their origin may be. A study of the literature and of my material makes an origin according to the second theory seem evident. At least some of the Aschoff cells arise from existing fixed and fully developed connective tissue cells. The Aschoff cell is probably not a specific type of cell called out by the rheumatic virus, but is the same as the polyblast found in any other form of proliferative inflammation.

While the typical nodular area of inflammation is found more commonly associated with acute rheumatic fever than with any other infectious process, it is doubtful whether it should be looked on as a specific anatomic lesion in the sense that the tuberculous or the syphilitic lesion is. The nodules cannot be said to have distinctive histologic characteristics. They are localized areas of proliferative and exudative inflammation, often with central areas of necrosis and with serous and fibrillar exudation. They show a decided variation in structure from a few cells to a diffuse inflammation and a marked variation in the kinds and number of cells composing them. The nodules are not present in all cases of rheumatic fever. They are frequently found in cases of



subacute bacterial endocarditis, a disease that is known to be produced by streptococci. Nodules, apparently typical Aschoff bodies, are at times found in nonrheumatic infections, as, for example, scarlet fever and syphilis.

The fact that experimental proliferative areas of inflammation so similar to the rheumatic nodules in rheumatic fever in man have been repeatedly produced in the heart, the subcutaneous tissues and the arteries by the injection of streptococci also suggests some objection to the belief that the Aschoff nodule represents a specific lesion produced by an unknown virus.

In conclusion, it may be said that the rheumatic nodule, called the Aschoff body when seen in the myocardium, is a small, fairly well localized area of inflammation, mostly proliferative, but at times chiefly or entirely exudative. The proliferative part of the nodule is composed of mononuclear and multinucleated cells, which vary in size, in shape and in the degree to which their cytoplasm takes the basic stain. The nuclei of these cells, as a rule, are vesicular in character. The cells appear to be modified polyblasts. The exudate consists mainly of lymphocytes, eosinophils and a varying number of polymorphonuclear leukocytes. An association of the proliferative and exudative reactions in varying degrees and combinations is commonly observed, and at times the nodule may closely simulate the abscess.

#### SUMMARY

The rheumatic nodule is most prominent in the heart and the subcutaneous tissues, but a similar nodular or diffuse inflammatory reaction is not infrequently found in the joints, the tendons, the galea aponeurotica, the diaphragm, the tongue and other muscles, the arteries, the heart valves in endocarditis and the tonsils.

The nodule may consist of but few cells surrounding small vessels; it may have a roset, fan or fusiform shape, or it may become irregular and so extensive as to form a diffuse interstitial myocarditis.

Often, but not always, the rheumatic nodule has a peripheral zone of proliferative or exudative cells and a central zone of necrosis. The cellular content consists of large mononuclear and multinucleated cells, lymphocytes, plasma cells, eosinophils and, in many cases, from a few to so many polymorphonuclear leukocytes that the nodule resembles an abscess. The large so-called Aschoff cells appear to have their origin from the histiocytes and to be but various forms of polyblasts.

The type of inflammation found in the rheumatic nodule in man cannot be said to be characteristic. In a relatively high percentage of cases of acute rheumatic endocarditis, the Aschoff nodules are not found in the myocardium. They are not infrequently found in the heart in cases of nonrheumatic infectious diseases. Nodular areas with a

cellular content similar morphologically and similar in staining characteristics have frequently been produced experimentally in rabbits by the injection of streptococci.

The rheumatic nodule appears to be a fairly well localized area of inflammation, mostly proliferative in character, but at times chiefly exudative.

It is doubtful whether the Aschoff nodule should definitely be considered a specific lesion resulting from a specific rheumatic virus.

## Notes and News

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**University News, Promotions, Resignations, Appointments, Deaths.**—James C. Small, director of the laboratories of the Philadelphia General Hospital, has resigned to engage in the private practice of medicine.

The Prince of Monaco Prize of the Academy of Medicine in Paris has been awarded to A. Borrell, director of the Institut d'Hygiene in Strasbourg, for his work on the etiology of cancer.

Jean R. Oliver, professor of pathology, Stanford University, has been appointed to the chair of pathology in Long Island Hospital Medical College, succeeding Archibald Murray.

Isabel H. Perry and Adelbert M. Moody have been appointed instructors in pathology in the medical school of the University of California; Zera E. Bolin has been promoted to assistant professor.

Esmund R. Long, professor of pathology, University of Chicago, has been appointed editor of the *Journal of Outdoor Life*, published by the National Tuberculosis Association.

Edward Francis of the Hygienic Laboratory of U. S. Public Health Service has been awarded the degree of Doctor of Laws by Miami University, Oxford Ohio.

Walter T. Harrison, U. S. Public Health Service, is the fifth member of the staff of the Hygienic Laboratory to suffer an attack of undulant fever contracted in the course of work with *Bacillus melitensis*.

Lawrence Parsons has been appointed instructor and Joseph C. Vintez demonstrator in pathology in the University of Southern California.

A chair of public health and hygiene has been established in the University of Virginia, and Kenneth F. Marcy of the U. S. Public Health Service has been appointed the first incumbent.

Claribel Cone, Baltimore, at one time professor of pathology in the Woman's Medical College, Baltimore, and well known art connoisseur, has died.

The death is reported of Benjamin Meade Bolton, pathologist to St. Joseph's Hospital, Paterson, N. J., at the age of 72. Dr. Bolton was formerly professor of pathology and bacteriology at the University of Missouri and at the St. Louis University.

F. Klopstock has been appointed chief of the division of immunochemistry of Kaiser Wilhelm-Institut für Biochemie in Berlin-Dahlem, Germany.

It is reported that Pierre Marie of the Pasteur Institute in Paris has died at the age of 38 from botulism accidentally acquired while working on the botulinus toxin.

William G. Hibbs has resigned as pathologist to the Norwegian-American Hospital in Chicago, and Hamilton R. Fishback has been designated to fill the vacancy.

**Committee of U. S. Senate on Cancer Research.**—Senator Wesley Jones, chairman of the Senate Commerce Committee and its subcommittee on cancer, has mailed to a number of scientists copies of a hitherto unpublished report by a conference on cancer called by the Public Health Service in April, 1928. In this report it is suggested that the Public Health Service could carry on research on cancer along four lines: statistics, occupational cancer, general biochemistry of the cell and radiation. This report will be discussed at hearings of the cancer subcommittee of the senate which are to be held in order to determine whether the federal government should make special provisions for work on cancer.

**Grants-in-Aid Fund of the National Research Council.**—The Rockefeller Foundation has made available a limited fund from which the National Research Council can make grants-in-aid of comparatively small amounts to support the research of individual American investigators and of special projects of restricted extent.

This fund will be administered by the council in much the same way that its funds for fellowships are now administered. A special committee has been established, composed of the chairman, the treasurer, the permanent secretary and the chairmen of the seven divisions of science and technology of the council. The committee will hold occasional meetings, beginning approximately October 1, to consider and pass on applications. Such applications should not be for fellowships, honoraria or publication costs, but may include field expenses. They should be made well in advance of the time of the intended use of the funds and should include detailed information as to the special qualifications of the applicant to pursue the investigations for which financial assistance is asked, and a statement of other support received or expected. The committee hopes that the universities and other interested organizations will cooperate with it in the proposed modest assistance of worthy research workers.

Correspondence should be addressed to the Secretary, National Research Council, Washington, D. C.

## Obituary

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PAUL A. LEWIS, M.D.  
1879-1929

Paul A. Lewis was born in Chicago, and took his medical degree at the University of Pennsylvania in 1904. While a medical student, he did advanced work in bacteriology and pathology. On graduation, he became resident in pathology at the Boston City Hospital and then assistant in the Massachusetts State antitoxin laboratory. In the years from 1906 to 1908, he was Austin teaching fellow in pathology at Harvard Medical School. During the next two years, he was assistant in pathology at the Rockefeller Institute in New York. He went from there to Philadelphia as director of the laboratory of the Henry Phipps Institute, later becoming also professor of experimental pathology in the University of Pennsylvania. In 1923, he became connected again with the Rockefeller Institute, this time as associate member attached to the department of animal pathology at Princeton, N. J., where he remained until his death. Dr. Lewis made important contributions to pathology, especially in the experimental field. With John Auer, he showed that acute anaphylactic death in the guinea-pig is caused by asphyxia from muscular spasm of the bronchioles. Working with Simon Flexner, he found that experimental poliomyelitis was inoculable from monkey to monkey indefinitely and caused by a filter-passing virus. At the Phipps Institute, he studied tuberculosis and made experiments with pure-line strains of guinea-pigs, on hereditary factors in the resistance to tuberculous infection. These illustrations of his work indicate his achievements as investigator. His interest in pathogenic viruses led him to volunteer for work on the yellow fever virus in Brazil and there he died an untimely death from yellow fever.



PAUL A. LEWIS, M.D.  
1879-1929



## Miscellany

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### REPRODUCTION OF PHOTOMICROGRAPHS

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# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

PAIN DUE TO TEMPORARY OCCLUSION OF THE CORONARY ARTERIES IN DOGS. J. FRANK PEAREY, WALTER S. PRIEST and C. M. VAN ALLEN, *Am. Heart J.* 4:390, 1929.

A method is described by which the coronary arteries in dogs may be occluded after the animals have recovered from the anesthesia of the preparatory operation. Sudden occlusion produced acute severe pain in dogs, the pain being continuous during the time of occlusion and ceasing immediately with the cessation of occlusion. The responses were due to real pain and not to cardiocirculatory failure or asphyxia.

PEARL M. ZEEK.

PRODUCTION OF PARTIAL LIVER INSUFFICIENCY IN RABBITS. PHILIP D. McMASTER and D. R. DRURY, *J. Exper. Med.* 49:745, 1929.

A rapid and simple method is described for the production of marked liver insufficiency in rabbits. The necessary operation can be carried out by an unassisted operator in a few minutes. The method should further the study of the physiology of the liver. The changes as concerns blood sugar, urea formation and uric acid metabolism would appear to be the same in the rabbit with hepatic insufficiency as in the dog.

AUTHORS' SUMMARY.

TOTAL SURGICAL REMOVAL OF THE LIVER IN RABBITS. D. R. DRURY, *J. Exper. Med.* 49:759, 1929.

A technic is described for the total removal of the liver of the rabbit without resultant circulatory difficulties. The method requires a preliminary operation to induce a development of portal and caval collaterals. Rabbits deprived of the liver in this manner, if given dextrose, live for varying periods up to forty hours. Before death, they show the same disturbances as do hepatectomized dogs. They die early of hypoglycemia, unless provided with sugar.

RELATION OF THE LIVER TO FAT METABOLISM. D. R. DRURY and PHILIP D. McMASTER, *J. Exper. Med.* 49:765, 1929.

Fat combustion is carried on adequately in rabbits deprived of the liver or brought into a condition of extreme liver insufficiency. Even twenty-four hours after hepatectomy, fat combustion goes on as well as in the normal animal. Evidently, the liver plays no essential part in the breaking down of fat.

AUTHORS' SUMMARY.

BIOMETRY OF CALCIUM, INORGANIC PHOSPHORUS, CHOLESTEROL AND LIPOID PHOSPHORUS IN THE BLOOD OF RABBITS. ALVIN R. HARNES, *J. Exper. Med.* 49:859, 1929.

Experiments are reported in which it was shown that the calcium, inorganic phosphorus, cholesterol and lecithin in the blood of normal rabbits were influenced by four types of light environment. The results of the experiments seem to warrant the following conclusions: Animals exposed to the ultraviolet light for a brief period each day give results that are diametrically opposite to those given by animals living in total darkness. The results obtained in animals exposed to the Cooper Hewitt light and in those living in the open laboratory are somewhat similar, but occupy a position between those obtained with an environment of darkness and with one of ultraviolet light. Animals do not immediately develop the characteristic effects of a particular environmental condition, but pass through a period of accommodation, which varies somewhat with different environmental conditions.

AUTHOR'S SUMMARY.

THE BLOOD IN OBSTRUCTION OF THE CARDIAC END OF THE STOMACH AND AFTER CLOSED-LOOP OBSTRUCTION OF THE JEJUNUM. RUSSELL L. HADEN and THOMAS G. ORR, J. Exper. Med. **49**:945 and 955, 1929.

The blood and the urine of the dog with experimental dehydration have been compared with the blood and the urine of the dog with obstruction of the cardiac end of the stomach. The average duration of life is slightly longer with dehydration than with obstruction. The urine output per kilogram of body weight is almost twice as great with dehydration as with obstruction. The increase in non-protein nitrogen and urea nitrogen is much the same in the two conditions, although somewhat more marked with obstruction. The chlorides of the blood are markedly increased with dehydration and slightly decreased with obstruction. The increase in fibrinogen and total protein is twice as great with obstruction as with dehydration. These observations indicate that there must be some factor or factors in addition to dehydration producing the toxemia of cardiac obstruction. The chemical observations in the blood of six dogs each with an obstruction of the upper part of the jejunum resulting from closed loops are reported. The duration of life in dogs with closed loops is less than in those with simple obstruction. All animals show a marked rise in nonprotein nitrogen and urea nitrogen, and a fall in chlorides. Usually the carbon dioxide combining power of the plasma is increased. The observations in closed-loop obstruction are essentially the same as in simple intestinal obstruction.

AUTHORS' SUMMARY.

PHYSIOLOGY AND PATHOLOGY OF RESORPTION OF CRYSTALLOIDS FROM THE PLEURAL CAVITY. J. F. BRODSKY, Ztschr. f. d. ges. exper. Med. **61**:24, 1928.

Potassium ferrocyanide is rapidly resorbed from the pleural cavity of the dog and may be demonstrated in the urine within from five to nine minutes after intrapleural injection. The pathways of resorption were studied by the intravenous injection of formaldehyde containing  $\text{Fe}_2\text{Cl}_6$ , which forms a blue precipitate (Berlin blue) with potassium ferrocyanide. The pleural surfaces were deeply stained, but no Berlin blue was found in the lung tissue proper, showing that resorption from the pleura of potassium ferrocyanide is not accomplished by the blood or lymph channels of the lung. Under physiologic conditions, crystalloids are resorbed by the lymph channels of the mediastinum, which may be regarded as the important drainage system of the pleural cavities. When the lymph channels of the mediastinum are inadequate, resorption may also take place through the lymphatics of the diaphragm, the pericardium, the visceral pleura and, rarely, the parietal pleural.

BALDUIN LUCKE.

EXPERIMENTAL AMYLOIDOSIS. F. R. REUTER, Ztschr. f. d. ges. exper. Med. **61**:347, 1928.

It has been claimed (by Domagk, Jacobs) that amyloid may be experimentally produced within a few minutes after injection of various micro-organisms. Reuter repeated Domagk's experiments, using a series of eighty mice, with negative results. One series of animals received a single intravenous injection of living *Staphylococcus aureus*. Other series received repeated intravenous or intraperitoneal injections of *Staphylococcus aureus* killed by heat; after sensitization, they received an intravenous injection of living *Staphylococcus*. The animals were killed within a few minutes after the injection. No substance resembling amyloid was found.

BALDUIN LUCKE.

EFFECTS OF EXTERNAL CHILLING ON RENAL FUNCTION. G. SCHLOMKA, Ztschr. f. d. ges. exper. Med. **61**:405, 1928.

The experiments were conducted on thirty-seven practically healthy boys and men between the ages of 12 and 30 years. Each was given, to drink, from 50 to

75 cc. of tap-water every ten minutes. The bladder was emptied every half hour. Two or three hours after the beginning of the experiment, venous stasis was induced in the legs by a rubber tourniquet, and the legs were then immersed in iced water, having a mean temperature of 2.5 C., for an average of sixteen minutes. In three fourths of the subjects, the amount of urine decreased about 30 per cent, while its concentration increased. In the urine of about one third of the patients, definite traces of albumin appeared temporarily. Generally, these "chilling reactions" took place after and not during the exposure. Without venous stasis, peripheral chilling had little effect on renal function.

BALDUIN LUCKE.

IS EDEMA THE RESULT OF CAPILLARY SECRETION? G. VON FARKAS, *Ztschr. f. d. ges. exper. Med.* **62**:35, 1928.

The venous pressure and the osmotic pressure of the blood colloids were determined in a number of edematous, as well as nonedematous, patients. It was found that increase of the venous pressure or decrease of the osmotic pressure of the blood proteins was generally associated with edema. Farkas concludes that cardiac edema is generally produced through a rise in venous pressure, while nephritic (the abstractor believes that this should read nephrotic) edema and cachectic edema are the result of lowered osmotic pressure of the blood colloids. This study emphasizes that disease of the capillary walls is not a primary requisite in the formation of edema.

BALDUIN LUCKE.

RETICULO-ENDOTHELIAL SYSTEM AND CARBOHYDRATE METABOLISM. F. Venulet, *Ztschr. f. d. ges. exper. Med.* **63**:720, 1928.

Blockage of the reticulo-endothelial system of dogs by means of a colloidal silver preparation (2 per cent collargol solution) leads to a marked hyperglycemia, which continues for several hours. Removal of the spleen, which corresponds to a partial blocking of the reticulo-endothelial system, likewise calls forth hyperglycemia; blockage of splenectomized animals increases the hyperglycemia only to an unimportant degree. After blockage there takes place a pronounced depletion of glycogen in the liver. The hyperglycemia induced by blockage of the reticulo-endothelial system is diminished in direct ratio to the reductions of the glycogen storage through starvation, epinephrine or phlorhizin. The degree of the glycogen storage, therefore, determines the magnitude of the induced hyperglycemia. In dogs treated with insulin prior to the blockage of the reticulo-endothelial system, no hyperglycemia occurs; removal of the thyroid likewise prevents a rise in level of blood sugar. However, if thyroidectomized dogs are fed with thyroid extract, a well marked hyperglycemia follows blockage. The hyperglycemia induced by blockage is associated with an increase of blood calcium and a decrease of potassium; there occurs a simultaneous lowering of the blood alkali reserve. The vegetative nervous system plays a rôle in blockage hyperglycemia.

BALDUIN LUCKE.

ABSORPTION ABILITY (PHAGOCYtic ABILITY) OF THE SURVIVING LIVER. E. J. STERKIN, *Ztschr. f. d. ges. exper. Med.* **63**:775, 1928.

The purpose of the experiments was to determine whether the reticulo-endothelial system preserves its phagocytic ability in surviving organs. The animals (dogs) were killed by exsanguination without previous narcosis. The liver (and in some experiments, the spleen) was removed, cannulas were tied into the afferent and efferent vessels and the organ was then perfused with a colloidal silver preparation. The amount of silver was estimated in the perfusate by colorimetric, as well as by analytic, methods.

The distribution of the retained silver was determined by histologic examination. It was found that most of the silver was precipitated on the vessel walls, and little was ingested by the Kupffer cells. From this, the author concluded that the phagocytic ability of the surviving liver differs from that of the organ in the living animal.

BALDUIN LUCKE.

## Pathologic Anatomy

TRAUMATIC NECROSIS OF THE SUBCUTANEOUS FAT OF THE NEW-BORN INFANT.  
LEON DE VEL, *Am. J. Dis. Child.* **37**:112, 1929.

A case of traumatic necrosis of the subcutaneous fat of the new-born infant is presented, with clinical and histologic observations. The symptomatology, pathology and etiology of the condition are reviewed.

AUTHOR'S SUMMARY.

THE DECIDUAL REACTION IN EXTRA-UTERINE PREGNANCY. B. S. KLINE,  
*Am. J. Obst. & Gynec.* **17**:43, 1929.

From a study of seventy-four cases, Kline found evidences supporting the belief that a decidual reaction of a greater or less extent occurs at the site of implantation. The termination of tubal pregnancy by hemorrhage depends on the inability of the scant decidua present to prevent invasion of the trophoblast into the blood vessels. The decidual tissue at the site of implantation persists only as long as the chorionic villi are intact; but that present elsewhere, such as in other portions of the tube and lining the uterus, though not constantly present, may persist after involution of the local decidual tissue has taken place.

A. J. KOBAK.

RELATION OF ECTOPIC GESTATION TO THE ASSOCIATED UTERINE CHANGES AND VAGINAL BLEEDING. SAMUEL H. GEIST and MORRIS R. MATUS, *Am. J. Obst. & Gynec.* **17**:151, 1929.

Geist and Matus studied thirty-nine cases of ectopic pregnancy in which the endometrial tissue was available for study. From this study uterine bleeding was found to be due to the following causes: (1) trauma, wherein the patient believing herself to have a normal pregnancy has attempted to induce abortion (two cases); (2) casting off of the uterine decidua which is associated with or preceded by bleeding and is initiated by the actual death of chorionic tissue, and (3) spotting, which was probably caused by uterine contractions initiated by efforts of the tube to expel its contents rather than death of the ovum.

A. J. KOBAK.

SPINDLE CELL SARCOMA OF THE KIDNEY IN ADULTS. H. L. KRETSCHMER and H. S. RANDOLPH, *Ann. Surg.* **88**:1033, 1928.

The case is interesting because of its rarity. In 97,000 autopsies reported by Lubarsch only four instances were found. The case occurred in a man, aged 55, with a large tumor mass in the left kidney weighing 750 Gm., composed of closely packed spindle cells. A brief description of eleven cases from the literature is appended.

N. ENZER.

ADENOCARCINOMA OF THE TESTIS IN THE ADULT. A. R. STEVENS and J. EWING, *Ann. Surg.* **88**:1074, 1928.

This is a report of a tumor removed from a man 51 years of age, which had a glandular structure due to the arrangement of the cells on a papillary stroma. The tumor grew slowly and metastasized slowly, and the authors hold that it should be differentiated from the embryonal carcinoma.

N. ENZER.

MESENTERIC INJURIES AND INTESTINAL VIABILITY. T. C. BOST, *Ann. Surg.* **89**:218, 1929.

This is a brief inquiry into the question as to how much intestine may be deprived of its circulation from the mesentery and yet survive. Case reports of three patients are recorded, in whom from 3 to 8 inches (from 7.6 to 20.32 cm.) of mesentery had been torn from the intestinal border. Also, in three dogs 6, 8 and 10 inches (15.24, 20.32 and 25.4 cm.) of mesentery were separated from the intestine. The patients and the dogs recovered after the mesenteric vessels had

been tied; the border of the intestine resutured, and the omentum tacked around the loop. It remains unsettled as to how much vascular recovery takes place through the omentum in these instances. The problem seems to have clinical significance.

N. ENZER.

SUBCUTANEOUS RUPTURE OF THE STOMACH. O. GLASSMAN, *Ann. Surg.* **89**:247, 1929.

The author has collected from the literature the reported cases of spontaneous and traumatic rupture. The latter he divides into those resulting from severe trauma and those resulting from moderate or slight trauma. A further group of spontaneous rupture seems to be related closely to those classified under slight trauma. The lacerations vary in size, and in the cases reported an explanation is not forthcoming. The combined effect of undue distention with acute local changes seems to obtain. In the instances of spontaneous rupture, the mechanical effect of acute distention seemed to be insufficient. Some local change, such as acute ulceration, would seem to be necessary. The article is valuable for its appended list of cases and excellent bibliography.

N. ENZER.

MYOMA OF THE APPENDIX. A. R. KOONTZ, *Ann. Surg.* **89**:272, 1929.

Fourteen cases of myoma of the appendix are tabulated, including the author's. In this instance, the myoma was diffuse in the muscular coat.

N. ENZER.

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX. J. SELINGER, *Ann. Surg.* **89**:276, 1929.

This review might better be entitled "Carcinoid of the Vermiform Appendix." This term has been applied to the curious tumor of the appendix in preference to the author's title, because it immediately distinguishes it as a nonmalignant one and probably of an entirely different fundamental nature. The author ascribes the first authentic description of this condition to Beeger in 1882. In 1926, about 300 cases had been reported. The author adds thirty-four cases.

N. ENZER.

DIABETES MELLITUS: A STUDY OF ONE HUNDRED AND FORTY-SEVEN AUTOPSIES. WILLIAM F. GIBB, JR., and VICTOR W. LOGAN, *Arch. Int. Med.* **43**:376, 1929.

A study of 147 cases of diabetes mellitus in which autopsy was performed was made with particular reference to the pathologic structure of the pancreas and the clinical course of the disease. Interstitial pancreatitis was found in 123 cases, 79 of which showed well advanced lesions. While this condition is more frequently present in older persons, it is often found in middle-aged persons. An explanation for this is offered in six cases showing acute inflammation of the interstitial tissue of the pancreas. A direct relation was found between the incidence of interstitial pancreatitis and lesions of the insular tissue (table 2). Tuberculous lesions in the pancreas were not found in any case. Lipomatosis of the pancreas is a late result of atrophy of the acinar tissue due to interstitial pancreatitis. Definite lesions of the islands of Langerhans were found in all but eleven of the cases studied. These lesions varied from difference in the staining reactions of the cells to fibrosis of the islands and hyaline degeneration. One case of calcified islands was seen. No relation was found between the type of cases in which gangrene was present and the degree of damage to the islands. The same is true of coma. An analysis of eleven cases without apparent damage to the islands showed that six patients did not have glycosuria when placed on a diet without insulin. It is hoped that a simple test may be devised to enable one to correlate the severity of the diabetic condition. Until this has been done, it seems impossible to relate the clinical and pathologic observations in diabetes mellitus.

AUTHORS' SUMMARY.

COARCTATION OF THE AORTA: A CASE OF THE ADULT TYPE IN A CHILD SIX MONTHS OF AGE. A. M. SALA and I. NACHAMIE, *Arch. Int. Med.* **43**:420, 1929.

Coarctation of the aorta may be either "infantile" or "adult." The first term is applied to those cases presenting a diffuse narrowing of the fetal isthmus; the second, to those presenting a relatively abrupt stricture, varying in degree, in the vicinity of the ligamentum arteriosum. A child, 6 months old, who was admitted with a bronchopneumonia of at least two days' duration, died some hours after admission. The developmental and family history was negative, but the infant had been ill with diphtheria and discharged from the hospital as cured eighteen days previous to second admission. No cardiac signs were elicited on examination because of the masking signs of bronchopneumonia. Autopsy revealed, in addition to an extensive bronchopneumonia, a localized necrosis of the left bronchus and a coarctation of the aorta of the "adult" type. This was accompanied by a patent foramen ovale, a moderate dilatation above and below the stricture and a moderate hypertrophy of the left side of the heart.

AUTHORS' SUMMARY.

ALZHEIMER'S DISEASE. WILLIAM MALAMUD and K. LOWENBERG, *Arch. Neurol. & Psychiat.* **21**:805, 1929.

Alzheimer's disease is considered a form of senility, or rather presenility, as it usually occurs in persons between the ages of 56 and 63. Malamud and Lowenberg report two cases; one patient died at the age of 65 (date of onset four years previously), the other at the age of 23 (duration about nine years). The first case presented a rather typical picture: mental confusion; memory defect; asthenia with inability to work; apraxia; speech disturbances, especially in the form of logoclonia (repetition of words); extreme untidiness, and complete disorientation. In the second case, the symptoms were approximately the same but the speech disturbances were not described, though they were present. The authors themselves doubt whether the second case should be classified as Alzheimer's disease, especially in view of the very young age of the patient and the long remission—four years' duration. However, the pathologic changes were alike in both cases—senile plaques practically all over the cortex, especially in the Ammon's horn but absent, in the first case, in the occipital lobe; so-called Alzheimer's fibrillary changes of the ganglion cells when stained with the method of Bielschowsky; cell destruction in the putamen and marked changes in the choroid plexus (which they classify as primary vascular disease, thrombosis of the capillaries with secondary changes in the form of connective tissue hyalinization and proliferation, and general hyperplastic transformation of the entire organ). The tufts or their cells showed hardly any significant changes. Those that were present were considered by them secondary. In the second case no normal plexus tissue was present. Scarlet red or sudan III have been used only in case 1. In view of the observations in these two cases they are inclined to accept Kraepelin's view that Alzheimer's disease may be independent of the senile group and that it may occur at any age.

G. B. HASSIN.

UNILATERAL NEUROFIBROMATOSIS OF THE CRANIAL AND DEEP CERVICAL NERVES. GEORGE T. PACK, *Arch. Neurol. & Psychiat.* **21**:919, 1929.

A boy, aged 11, of average intelligence, had an overgrowth of the left side of the face, pain and partial blindness in the left eye and daily vertigo. At the age of 2 months a fixed enlargement of the left pupil appeared, and at the age of 4 months the soft parts of the left side of the face became noticeably enlarged, and progressed gradually during the next ten years. The neurologic examination revealed exophthalmos of the left eye, probably caused by a retrobulbar tumor, and a mild keratoglobus; the left pupil was dilated and fixed; the retina (left?) was undergoing atrophy and the blood vessels were collapsed, except near the disk where they were engorged. The left side of the face was swollen and numerous

discrete, freely movable tumor masses were present in the left upper eyelid, left cheek and the left side of the neck, particularly on the posterior cervical triangle and along the anterior border of the sternocleidomastoid muscle. There was marked asymmetry; the thorax, scapula, pectoral muscles, leg and arm were much smaller on the left side than on the right. Roentgenogram of the skull revealed the left orbit to be smaller than the right and the left antrum "abnormal in size and location." The examination of an excised nodule (from the neck) showed it to be rather avascular, surrounded by a capsule and pierced, as it were, by nerve fibers. The latter were dissociated by the intervening prolongations of the capsules. The major portion of the tumor consisted of fibroblasts, and most of the nerve fibers were deprived of their myelin. Some portions of the tumor mass exhibited mucoid degeneration. It was impossible to ascertain whether or not the connective tissue cells were neuroglia cells from the sheath of Schwann. In some areas, the cells were "in anastomotic chains." The author comments on the possibility of the effect neurofibromatosis may have on the bones, that the bone changes observed in this patient might have been caused by neurofibromatosis. G. B. HASSIN.

**SYNDROME OF TUMOR OF SPINAL CORD DUE TO ADENOCARCINOMA MUCOSUM OF THE PAROTID GLAND WITH GENERAL METASTASIS.** J. L. GARVEY, Contributions to Medical Science Dedicated to A. S. Warthin, Ann Arbor, George Wahr, 1927, p. 661.

Garvey records a case of primary adenocarcinoma mucosum of the parotid gland which gave the first evidence of metastasis eight years after operation on the primary neoplasm, when symptoms and signs of localized compression of the spinal cord appeared. Postmortem examination revealed extensive metastasis to the vertebrae, femora, calvarium, sternum, clavicle, lungs, liver, retroperitoneal lymph nodes and suprarenal glands.

WALTER M. SIMPSON.

**THE PITUITARY ADAMANTINOMA.** M. M. PEET, Contributions to Medical Science Dedicated to A. S. Warthin, Ann Arbor, George Wahr, 1927, p. 673.

Peet describes two cases of adamantinoma of the pituitary region. One, a typical adamantinoma of craniopharyngeal duct origin, was primarily intrasellar, the tumor apparently having its origin in the extreme lower end of the infundibular stalk; the other tumor, an adamantinocarcinoma, arose from the extreme upper end of the infundibulum. A typical Fröhlich syndrome developed in the first case.

WALTER M. SIMPSON.

**REACTIONS OF THYROID TO INFECTIONS ELSEWHERE IN THE BODY.** WARREN H. COLE and NATHAN A. WOMACK, J. A. M. A. 92:453, 1929.

In septic and toxic processes there may be hyperplasia, loss of colloid, desquamation and decrease in iodine in the thyroid. Experimental data also support the idea that the thyroid takes an active part in reactions due to infection and toxic action.

**GAUCHER'S SPLENOMEGALY.** NATHAN ROSENTHAL and B. S. OPPENHEIMER, J. A. M. A. 92:637, 1929.

Roentgenographic changes in the bones in the course of Gaucher's disease are not uncommon, and are of value in establishing the diagnosis. In six of our eight cases which were examined by the roentgen rays, characteristic bone changes were found. The commonest early change was a fusiform expansion of the lower third of the femurs. Gross skeletal changes, such as gibbus and pathologic fractures, are rare. We have observed only one well marked instance. Gaucher's disease, Niemann-Pick's disease and possibly the infantile form of amaurotic family idiocy (Tay-Sachs) are congenital, familial, constitutional disturbances of lipid metabolism. Splenectomy in Gaucher's disease cannot be considered a

curative measure. It may, however, be of value in relieving the anemia, the hemorrhagic diathesis or the burden to the patient of the spleen itself.

## AUTHORS' SUMMARY.

CALCIFICATION OF THE VESSELS IN DIABETES. L. B. MORRISON and I. K. BOGAN, J. A. M. A. **92**:1424, 1929.

Roentgenographic evidence of calcification of the vessels was present in the legs in 53 per cent of 324 diabetic patients varying in age from 2 to 81 years. In the third decade 6 per cent of the patients showed vascular calcification, and in the seventh decade 87 per cent. Twenty-one per cent showed advanced calcification. Advanced calcification was not found in patients under 40 years of age, although definite calcification was present in five cases. No case of gangrene was found in a patient under 40 years of age. Syphilis, dental infections and arthritis appear to play no part in the production of vascular calcification in this series. Seventeen per cent of patients without calcification (average age, 41 years) and 49 per cent of those with calcification (average age, 59 years) have blood pressure over 150. Patients over 50 years of age with sclerosis are about twice as apt to have high blood pressure as those without calcification. Six, or 9 per cent, of the patients with diabetes of ten years' duration did not show calcification.

## AUTHORS' SUMMARY.

EFFECT OF COPPER ON THE LIVER. FREDERICK B. FLINN and WILLIAM C. VON GLAHN, J. Exper. Med. **49**:5, 1929.

Copper, or its compounds used, does not cause the deposition of pigment in the livers of rabbits, guinea-pigs or rats. Neither does it produce a cirrhosis in these animals. Spontaneous deposition of pigment occurs frequently in the livers of normal rabbits on the usual laboratory diet. The feeding of a diet of carrots exclusively will produce deposition of pigment in the livers of rabbits, in every way identical with that ascribed to copper. The pigment deposited in the livers of rabbits is probably of exogenous origin.

## AUTHORS' SUMMARY.

THE LYMPHATIC TISSUE. WILLIAM EHRLICH, J. Exper. Med. **49**:347 and 361, 1929.

1. *In Subcutaneous Infection with Staphylococci.*—On subcutaneous infection of rabbits with staphylococci of low virulence there appears at the place of injection first a hemorrhagic purulent inflammation and later a localized purulence. In the regional lymph nodes there is lymphatic hyperplasia, and in the blood a lymphocytosis. In the regional lymph nodes there is first a regressive change of Flemming's secondary nodules and of transmission forms. Then follows lymphatic hyperplasia, starting apparently from solid secondary nodules and progressing by way of pseudo-secondary nodules to a diffuse lymphoid hyperplasia. The increase of lymphocytes in the blood parallels this development. Only after the highest point of the lymphocytosis has been reached or passed are the first Flemming's secondary nodules found, which thereafter increase in number and size while the number of lymphocytes in the blood falls, and reach their maximum development when the number of lymphocytes in the blood is again normal. Therefore, the original conception of Flemming that the site of formation of the lymphocytes of the blood is in Flemming's secondary nodules, cannot be accepted. The lymphocytes of the blood originate in the pseudo-secondary nodules as in embryonic life. The mother cells of the lymphocytes would appear to be Marchand's proliferating endothelial (reticular) cells.

2. *After Intravenous Injection of Killed Staphylococci.*—In eighty-seven rabbits, some of which received intravenously at various intervals small doses of killed staphylococci and others large doses, the following observations were obtained. There occurred a hyperplasia of lymph nodes, spleen and thymus, that is to say, a status thymicolymphaticus. This phenomenon is explained as due to immediate



local irritation caused by bacteria and their products and by certain "toxins," partly of exogenous, partly of endogenous, origin. The lymphocytosis which appeared was parallel in time and degree with the hyperplasia of the peripheral lymph nodes (axillary, popliteal and cervical lymph nodes) and probably originated in the pseudo-secondary nodules of these nodes. There occurred intense mesenchymal reaction in the vascular connective tissue of the lungs, liver and spleen, and after large doses slighter reactions in the suprarenals, kidneys and heart. These reactions correspond with Oeller's adventitial reactions and Siegmund's intima proliferations. In the interstitial tissue of these organs as well as in the walls of the minor vessels, proliferations of cells, partly of the type of lymphocytes and plasma cells, partly of that of histiocytes and reticulo-endothelial cells, appeared, which, after large doses, were mixed with many giant cells of Langerhans' type. After small doses, lymphocytes and plasma cells predominated; after large doses, histiocytes and reticulo-endothelial cells. Because these reactions occurred immediately after the first injection, they can be regarded as primary reactions of the organism to bacteria and their products.

AUTHOR'S SUMMARY.

CHRONIC NEPHRITIS INDUCED IN THE DOG BY URANIUM NITRATE. WILLIAM DEB. MACNIDER, J. Exper. Med. 49:387 and 411, 1929.

1. *Functional and Pathologic Study.*—Uranium nitrate in the dog induces an epithelial injury to the kidney which is largely localized to the proximal convoluted tubule epithelium. With the development of such structural changes in this tissue, functional alterations are induced in the glomeruli which later in the experiments are shown structurally by the formation of connective tissue in these units. The evidence of impaired renal function, other than the water elimination by the kidney, progressively increases as the epithelial injury becomes intensified. A certain number of dogs rendered acutely nephritic from uranium, after a variable period allowed for renal repair, returned to a complete functional normal. The commencement of such a restoration in function is coincident with the development of the process of epithelial repair in the injured tubular epithelium and at the same time with the development of histologic evidence of structural changes in the glomeruli. The ability of such animals to effect a restoration in normal renal function depended on the completeness and type of epithelial repair which develops and not with the degree to which connective tissue formation and obliteration of glomeruli have failed to develop. A final group of animals, after having developed acute nephritis, were unable to effect such changes of repair in the kidneys that a normal functional state could be established. These animals showed the anatomic characteristics and the functional expression of a chronic nephritis. Such a failure to return to a state of functional normal has been associated in them with the regeneration in the proximal convoluted tubules of a predominant type of epithelium which is atypical for the tubules in this location and with the development of structural changes in the smaller arteries of the kidney and obliterative changes in the glomeruli. The study as a whole emphasizes the functional value of the proximal convoluted tubule epithelium during periods of acute renal functional depression, when such periods are recuperated from with the establishment of a state of normal renal function, and in conditions in which without a complete restoration of function a functional improvement has developed with the establishment of a chronic nephritis.

2. *Response of Kidney to Second Injection of Uranium Nitrate.*—Uranium nitrate in the dog has a high degree of selective affinity as a nephrotoxic for the epithelium of the proximal convoluted tubules. The glomeruli participate in the injury and develop obliterative connective tissue changes as evidence of a pre-existing acute injury followed by repair. The repair to the degenerated tubular epithelium is accomplished by two processes. First, by a regeneration of convoluted tubule cells from such cells not too severely injured in this location. This type of regenerated epithelium has no resistance to uranium. Second, the regeneration may occur as an ingrowth of cells or as syncytial buds from cells in the terminal portion

of the proximal convoluted tubule or from the upper end of the descending limb of Henle's loop. This type of regenerated epithelium which is entirely different cytologically from normal convoluted tubule epithelium is resistant to a second injury from uranium even when the amount of this nephrotoxic agent has been increased to double the amount of the initial injection. The kidney does not develop a local tissue immunity or resistance to uranium in the sense that cells of the same type once injured by it acquire as a result of the injury a resistance. The resistance and apparent but not real immunity is due to another type of cell with resistance having been substituted for a cell with but little resistance. This fact may be looked on as constituting part of a defense mechanism in the kidney and may in part explain the long duration of certain types of chronic nephritic processes. The functional studies which have been made during the initial injury from uranium to the tubules and during the secondary injury in animals which have either shown a resistance or a lack of resistance, emphasize the importance of the tubular epithelium as a part of a secretory mechanism in urine formation. During periods when the proximal convoluted tubule epithelium is in a state of acute degeneration there is a disturbance in the acid-base equilibrium of the blood, a reduction in the elimination of phenolsulphonphthalein and a retention of urea nitrogen, nonprotein nitrogen and creatinine. When this epithelium is regenerated by the formation of a tubular epithelium normal in character for this location of the tubule, regardless of structural changes in the glomeruli, the foregoing evidence of renal dysfunction returns to the normal. If at such a period this type of regenerated epithelium be injured by a secondary injection of uranium a state of acute renal dysfunction is induced in an intensified form. In those animals in which the repair to the tubules was accomplished by the formation of an atypical type of epithelium in the convoluted tubules as well as by the formation of cells normal in histologic appearance for this part of the tubule there was an improvement in the degree of depletion of the reserve alkali of the blood, in the elimination of phenolsulphonphthalein and in the retention of urea nitrogen, nonprotein nitrogen and creatinine. Certain of these values did not reach the normal. In such a state of renal repair when a second injection of uranium was given the kidney was found to have developed a marked resistance to it. There was but slight evidence of a depression in renal function. Associated with this acquired functional resistance there was no evidence of injury to the atypical, flattened regenerated epithelium of the proximal convoluted tubules.

AUTHOR'S SUMMARY.

OBSTRUCTION TO CARDIAC CORONARY SINUS. R. T. GRANT and T. DUCKETT JONES, *Heart* **14**:241, 1928.

One case is described in which the coronary sinus was occluded by a fibrous diaphragm apparently not due to a congenital malformation but to an old thrombus.

AUTHORS' SUMMARY.

HEART VALVE IRREGULARITIES IN RELATION TO SUBACUTE BACTERIAL ENDOCARDITIS. R. T. GRANT, J. EDWIN WOOD, JR., and T. DUCKETT JONES, *Heart* **14**:247, 1928.

Recesses, pockets, crevices and projections related to heart valves do not, in themselves, afford a foothold for bacteria. Degenerative changes in heart valves often lead to the deposition of small platelet thrombi on the surface and these thrombi offer passing organisms a nidus for their establishment. Therefore, if organisms invade the blood stream at a time when a thrombus is forming on a heart valve, the conditions are suitable for the development of bacterial endocarditis.

PEARL ZEEK.

CHRONIC APPENDICITIS. T. BHASKARA MENON, *Indian J. M. Research* **16**:656 and 661, 1929.

1. *The Lymphoid Tissue of the Appendix*.—A cross-section of a normal appendix shows on an average about six lymph follicles and three well defined

germ centers. In a chronically inflamed organ there is a tendency for atrophy of the lymphoid tissue to occur. Lymphoid cells are normally found in numbers in the submucous coat of the appendix. There is not any marked involuntary atrophy of the lymphoid tissue of the appendix in persons between the ages of 10 and 50. There seems to be a definite relationship between lymphoid hyperplasia of the appendix in children as well as adults and clinical symptoms of colicky pain in the lower part of the abdomen.

2. *Eosinophil Infiltration of the Appendix*.—Eosinophilia of the mucous membrane of the appendix is a normal phenomenon, at least in the tropics. Eosinophil infiltration of the submucosa of the appendix is evidence of chronic appendicitis.

#### AUTHOR'S SUMMARY.

THE MORBID ANATOMY OF SPRUE. F. P. MACKIE and N. H. FAIRLEY, Indian J. M. Research 16:799, 1929.

The changes in the tongue are those which have already been described by other observers. The mucous membrane is thinned and atrophic and the lingual papillae may disappear. There is desquamation of the epithelial layers and occasionally loss of tissue amounts to superficial ulceration with little sign of inflammatory reaction. The changes in the intestine are most marked in the ileum, but are present to some degree throughout the whole tract. They are chiefly those of thinning and atrophy of the mucous membrane with marked degeneration and ultimately the almost complete disappearance of the absorptive and secretory epithelium. Here again, the change is one of degeneration and aplasia, and if it is preceded by inflammation there is little evidence of such in the terminal stages of the disease. There is evidence of blood destruction in the mucosa suggesting the absorption of some hemolytic substance from the intestine and the destruction of blood in situ. The disposition of micro-organisms in the gut wall favors the view that there is antemortem invasion by bacteria such as is known to occur in conditions of malnutrition due to vitamin deficiency. A specify atrophy of cardiac muscle out of all proportion to any decrease explicable in terms of mere starvation was noted in two cases of our series. On the other hand, the depreciation in the weights of the other viscera—notably that of the liver, spleen and kidneys—can be explained on the latter basis. The liver, kidney and the suprarenals sometimes show microscopic changes of a degenerative nature such as might be induced by the action of a toxin. Iron pigment is laid down in moderate amount, especially in the liver, but not in the same quantities as characterize pernicious anemia. The bone-marrow as seen in the femur or tibia shows in most cases marked aplasia. The red marrow, when present, is much reduced in quantity, though in two instances there was extensive hyperplasia similar to that seen in pernicious anemia. A moderate grade of hyperplasia was seen in another case. Such observations suggest that in sprue there is a toxin which primarily stimulates and later leads to the exhaustion of the hemopoietic function, so that in terminal stages of the diseases an almost complete aplasia results. This supposition is borne out by the condition of the blood as seen during life. These and other studies lead us to believe that sprue is primarily a disease of the intestinal tract which, if progressive, results ultimately in degeneration and destruction of the absorbing and secretory tissues and the production of a condition of slow progressive starvation. The absorption of toxins from the damaged mucosa perhaps associated with actual bacterial invasion, appears to be an important factor in the progressive anemia and other late manifestations of the disease.

#### AUTHORS' SUMMARY.

CULTURES OF BLOOD LEUKOCYTES: FROM LYMPHOCYTE AND MONOCYTE TO CONNECTIVE TISSUE. ALEXANDER MAXIMOW, Arch. f. exper. Zellforsch. 5:169, 1928.

The lymphocytes and the monocytes of the mammalian blood in vitro are transformed in the course of a few hours into large, ameboid, phagocytic, dye-storing elements. These are identical in origin, structure and function with the

polyblasts or mononuclear exudate cells as found in inflamed tissue. Mitoses occur in the hypertrophying lymphocytes and monocytes, but are rare. In their transformation into polyblasts, the lymphocytes pass through a stage more or less similar to the monocyte. During the third to the fifth day of life in vitro, a large part of the polyblasts acquires a fibroblast-like aspect and structure. This condition is reversible. Under the influence of stimuli (strong light or, perhaps, heat) the cells rapidly contract, round off and again become ameboid. In later stages (from seven to twelve days), especially when cultivated in flasks, the fibroblast-like cells and many of the ameboid polyblasts are transformed irreversibly into typical fibroblasts. They lose the ability of motion, phagocytosis and storing of vital dyes. Their protoplasm develops tonofibrillae (fibrogia) which seem to arise through direct transformation of chondriosomes. These cells divide exuberantly by mitosis. First scattered singly at the periphery of the explant, they gradually assemble in groups and form strands and sheets. In still later stages (twelve to twenty-five to forty days) large cultures of connective tissue develop. They consist of fibroblasts and of resting polyblasts (histiocytes) scattered among the fibroblasts. The polyblasts gradually are transformed into fibroblasts in the same way as they do in the later stages of inflammation, in scar formation. The cultures thus obtained do not differ from connective tissue cultures of any other source. The histiocytic (polyblastic) and fibroblastic potencies of the lymphocytes of the blood are conclusively demonstrated. A large part of the lymphocytes of the blood of the chick in vitro turns into thrombocytes.

AUTHOR'S SUMMARY.

MAMMALIAN LYMPH IN TISSUE CULTURE: FROM LYMPHOCYTE TO FIBROBLAST.  
WILLIAM BLOOM, Arch. f. exper. Zellforsch. 5:269, 1928.

The lymph of the thoracic duct of the rabbit contains few cells other than various sized lymphocytes. When such lymph is cultured in vitro, large and small lymphocytes change into typical inflammatory mononuclears or polyblasts which store lithium carmine. This transformation usually happens within from six to eight hours; it can be followed in the living cultures stained with neutral red and in the sections of fixed cultures. After the first ten or twelve hours many of the lymphocytes die but the polyblasts continue to develop. In a few days more the polyblasts become very large and change into typical fibroblasts. These experiments clearly indicate the importance of the lymphocytes as a source of the exudate mononuclear cells (polyblasts) of inflamed tissues.

AUTHOR'S SUMMARY.

THE ORIGIN AND NATURE OF THE MONOCYTE. WILLIAM BLOOM, Folia haemat. 37:1, 1928.

An intense monocytosis is produced in rabbits either by infection with *B. monocytogenes* or by the intravenous injection of India ink, lithium carmine or saccharated iron oxide. In the latter experiments, the development of the monocytes into macrophages can be followed easily. The assumption found so frequently in the recent literature that monocytes arise directly from fixed cells—endothelium or reticulum endothelium—has not been demonstrated in any of the papers claiming this process. It was not demonstrable in my material. The monocytes develop by individual transformation of the lymphocytes in the blood stream, especially in the sinuses of the spleen and liver. In splenectomized rabbits, which were given injections of india ink into the portal vein and were then infected with *B. monocytogenes*, monocytes develop from hemocytoblasts in the bone marrow as well as from the lymphocytes in the lymph nodes. The monocytes should be sharply discriminated from free histiocytes, although they may develop into histiocytes in vivo and in vitro. Monoblasts do not exist. The so-called monoblasts of the literature are identical with lymphocytes when studied by any of the present hematologic and histologic methods.

AUTHOR'S SUMMARY.

THE CAUSE OF DEATH OF NEW-BORN CHILDREN. W. KLIMKE, *Klin. Wchnschr.* **8**:359, 1929.

In the Dortmund Institute the causes of death of new-born children from 1912 to 1914, inclusive, and from 1920 to 1928, inclusive (total 1,111), are: malformations, 6.2 per cent; birth traumas, 147 per cent; birth operations, 6.5 per cent; fetal complications (including diseases of all kinds), 20 per cent; maternal complications, 9.6 per cent; generalized atrophies, 22.2 per cent; unknown causes, 21.5 per cent. Congenital syphilis caused the death of 80. This as a cause diminished from 15.75 and 13.5 per cent in 1920 and 1922 to 0 per cent in 1928. Congenital pneumonia was observed in four stillborn and in eleven live-born infants. Aspiration pneumonia was found in nine new-born infants. Aspiration without reaction of the lungs caused the death of eighty-five stillborn and thirty-four live-born infants. Information regarding etiology was not obtained in six infants with generalized edema. Syphilis and nephritis were not present in the mother.

EDWIN F. HIRSCH.

SARCOMA OF THE VAS DEFERENS. W. KARO, *München. med. Wchnschr.* **76**: 374, 1929.

This is a brief account of a polymorph cell or spindle cell sarcoma of the right vas deferens. The tumor grew slowly over an interval of ten years.

EDWIN F. HIRSCH.

SPLENOMEGALY, A SYMPOSIUM. *Verhandl. d. deutsch. path. Gesellsch.* **23**:7, 1928.

W. Hueck, Leipzig, in discussing the anatomy of the spleen, in the first of twelve papers comprising the symposium, concluded that the blood courses through the spleen in a closed circuit at least in embryonic life. O. Lubarsch, Berlin, proposed the following grouping for splenic enlargements:

1. Splenomegaly in circulatory disorders.
  - (a) Disorders in systemic circuit.
  - (b) Disorders in portal circuit—thrombophlebitic splenomegaly.
2. Splenomegaly in blood diseases.
  - (a) Leukemia.
  - (b) Pernicious anemia.
  - (c) Hemolytic jaundice.
  - (d) Thrombopenic purpura.
  - (e) Erythremia.
  - (f) Splenogenous anemia.
3. Metabolic disturbances.
  - (a) Sugar and fat.
  - (b) Gaucher and Niemann-Pick.
4. Splenomegaly in combined circulatory and metabolic disturbances.
  - (a) Cirrhosis of the liver.
  - (b) Banti's disease.
5. Splenomegaly in infections and intoxications.
  - (a) Acute.
  - (b) Chronic as endocarditis lenta, tuberculosis, syphilis, malaria, kala-azar, etc.
6. Splenomegaly associated with tumors.
  - (a) Primary.
  - (b) Secondary.
7. Splenomegaly due to animal parasites.
  - (a) Echinococcus.

B. Ugriumaw, Leningrad, summarized the observations in sixty cases of splenomegaly. Of forty-three recorded cases the spleen weight was as follows: in three cases, from 500 to 1,000 Gm.; in twenty-three cases, from 1,000 to 2,000 Gm., and in seventeen cases, over 2,000 Gm. The largest spleen weighed 6,500 Gm. Fifty-five specimens were obtained from males; the small number from females apparently being due to the reluctance of Mohammedan women to permit observation by a physician. Half of the specimens were obtained from the bodies of persons from 20 to 40 years of age. In fifteen cases the liver was of normal size; in fourteen it was small, and in thirty-one it was enlarged. The only lymph glands found enlarged were the mesenteric, periportal and retroperitoneal. Histologically, it was found impossible to differentiate Banti's disease from hemolytic jaundice. R. Rössle, Basel, discussed the condition of the spleen following hemorrhage; stressed the analogy between the edematous pulp in this condition and in such things as acute infections and maintained the presence of a splenic enzyme in both conditions. In the discussion following the presentation of the foregoing papers additional interesting features were observed. Bürger saw splenomegaly occur four times in infections with Bang's bacillus in the Kieler clinic in 1927. Ingestion of contaminated milk was the cause of the illness in all instances and the serum of the patients agglutinated Bang's bacillus and the bacillus causing Malta fever in high dilutions. Bang's bacillus was cultured in the blood. The characteristic picture of splenic enlargement developed after many weeks of remitting fever and the splenic tumor receded very slowly after treatment. Weicksel, in studying the red blood cells and the function of the spleen in blood transfusion, produced anemia in dogs and then used transfusion. He concluded that the spleen acted as a reservoir for the red blood cells. To further prove this he took photographs of the spleen in two projections and found that immediately after the transfusion the splenic volume was reduced one-fourth while in from one to two hours it enlarged to a size larger than before the transfusion. Helly maintained the normal vascular system of the spleen was closed but thought tears in the delicate splenic capillaries might aid in producing extravasations. He also held that because of the delicate construction of the spleen, injection methods are likely to produce erroneous pictures. Schilling stressed the three tissue components of the spleen, namely, the myeloid, lymphatic and reticulo-endothelial; he spoke of the spleen as a sponge the meshes of which might become engorged with any one of the aforementioned tissues, and advocated specifying which elements were involved in every type of splenic enlargement. Hamperl illustrated with a case report the impossibility of distinguishing the two types of lipoid cell splenohepatomegaly, Gaucher's disease and Niemann-Pick's disease. A child, 5½ months old, clinically had a lipemia, and splenic puncture brought out cells from 30 to 60 microns in diameter, round or oval with one or more peripheral nuclei and a homogeneous protoplasm staining blue with Mallory's connective tissue stain. In addition, these cells were found post mortem in the liver, spleen, lymph glands, bone-marrow, lymphoreticulum of the tonsils and thymus and in the mucosal stroma of the small bowel near Peyer's patches. The distribution of these cells was in accordance with the Niemann-Pick type. Furthermore, chemical analyses of the organs seemed to bear this out as the total lipoids were 9.6 per cent, total cholesterol 0.93 per cent and phosphorus 5.98 per cent. To confuse the issue, however, large quantities of Guacher substance were found. Abrikosoff cited instances of chronic splenomegaly in which fungi of the *Aspergillus* type were encountered morphologically and culturally. Sternberg doubted the occurrence of the fungi. He had seen encrustations of iron phosphate in a markedly atrophic spleen, and noted the resemblance of these encrusted cords to fungi.

GEORGE RUKSTINAT.

CONCRETIONS OF THE CHOROID PLEXUS. FRANZ WINDHOLZ, *Verhandl. d. deutsche path. Gesellsch.* 23:296, 1928.

Three different types of calcifications occur in the choroid plexus: (1) round, lamellated concretions, (2) sclerotic calcium incrustations of villi of the plexus and (3) angiogenic and amorphous petrifications of the supporting framework of

the plexus. The calcifications of the psammoma bodies are due to changes in the colloidal state of the protein substances caused by their increased lipid content. The two last mentioned calcifications are of the dystrophic type in the presence of fat and fatlike substances. There is evidence of a marked fat and calcium metabolism of the plexus.

W. C. HUEPER.

THE CONDITIONS OF GROWTH IN TISSUE CULTURES. H. GUILLERY, Verhandl. d. Deutsche path. Gesellsch. **23**:301, 1928.

Tissue cultures of tissues of different proliferative activity grown in the same container show a gradual increase of the growth intensity of the more slowly growing cultures till it reaches that of the most rapidly growing culture. That this phenomenon is not caused by an exchange of growth substances between the cultures can be demonstrated by the separation of the individual cultures by glass plates, which do not interrupt the common plasma layer of the cultures. Glass plates placed between two cultures prevent this phenomenon. Metal mirrors placed at such an angle above a culture that rays emanating from the culture are reflected on another culture separated from the first one by a glass plate effect a reappearance of the phenomenon. The author concludes that radiating energy is responsible for the phenomenon in question.

W. C. HUEPER.

THE EFFECT OF VARIOUS EXOGENOUS FACTORS ON HOMOPLASTIC AND HETEROPLASTIC TRANSPLANTS. B. MORPURGE, Verhandl. d. deutsch. path. Gesellsch. **23**:330, 1928.

Skin grafts in rats of the same race are successful if the grafted animal is starved for several days and then insufficiently fed till the grafted tissue has become permanently attached. Grafts of guinea-pig skin on starved rats show a definite delay of necrosis. Similar results are obtained with animals fed with food heated to 150 C. for one hour and a half. Rats grafted with skin of animals of the same or different races and kept at temperatures ranging from plus 5 C. to minus 5 C. show similar good results.

W. C. HUEPER.

THE DISTRIBUTION OF VITAL STAINS IN THE BODY. L. LOEFFLER, Verhandl. d. Deutsche path. Gesellsch. **23**:336, 1928.

The author demonstrates in experiments with rabbits the dependency of the distribution of vital stains on the circulatory conditions in the different parts of the body. India ink injected into the vein of the ear is normally mainly retained in the spleen and liver. India ink injected with epinephrine is almost exclusively retained in the lungs. Similar differences are seen after injections into the mesenteric vein. Temporary ligation of the mesenteric artery preceding the injection of ink or simultaneous injection of histamine or chloroform produces similar results. Differences in the distribution of vital stains are seen if from 2 to 3 per cent solutions of trypan blue or lithiocarmine are used in conjunction with the aforementioned substances or procedures or after section of the ischiadic nerve. The dye particles are seen either in the cells or in clumps in the capillaries. Their location depends on the dispersity of the solution used and the colloidal status of the medium into which they are introduced. The particles of highly disperse solution enter the cells by diffusion, a purely physicochemical process, not by phagocytosis. The storage of granules of vital stains in the cells of the reticulo-endothelial system of the spleen and liver represents only one of the many possibilities in the distribution of vital stains.

W. C. HUEPER.

THE PATHOGENESIS OF THE TUBERCULOSIS IN OLD AGE. H. E. ANDERS, Verhandl. d. Deutsche path. Gesellsch. **23**:406, 1928.

The tuberculosis in old age represents a late manifestation of the tuberculous primary lesion if the quiescent primary lesion of the chronic tuberculosis of the lung

is not taken into consideration. A reactivated tuberculosis of the lymph node (lymphoglandular endogenous reinfection of Ghon) was present in 35 per cent of the bodies examined. The spreading of the reactivated process may occur in an ascending or descending direction. The danger of hematogenous metastasis is present in the ascending type of spreading. Numerous isolated hematogenous organic tuberculous foci were observed in 69 per cent of the glandular tuberculosis and in 30 per cent of the organic tuberculosis. The organ systems arranged according to frequency of affection are the bony system, the urogenital system, the central nervous system and the suprarenals. The appearance of the endogenous, lymphoglandular reinfection at the forty-fifth year of life seems to support the conception that the tissue immunity of the lymphoglandular component of the tubercular primary lesion decreases or disappears at this age in a certain percentage of persons.

W. C. HUEPER.

INTERRENALISM AND INTERRENAL INTOXICATION. E. VON GIERKE, *Verhandl. d. Deutsche path. Gesellsch.* **23**:449, 1928.

Pseudohermaphroditismus masculinus externus with cortical adenomas in both suprarenal glands and female secondary sexual characteristics in a person 62 years old is considered as the result of the action of the interrenal system during fetal life. Hyperplasia of the cortex of the suprarenal glands occurs in infants during the first weeks of life suffering from digestive disturbances, intestinal diseases and toxic symptoms. The hyperplasia is either a nodular formation of lipoid cells or a diffuse hyperplasia of the cortex. Pseudohermaphroditism may be present or absent.

W. C. HUEPER.

DEVELOPMENT OF MACROPHAGES. M. SILBERBERG, *Verhandl. d. Deutsche path. Gesellsch.* **23**:456, 1928.

Silberberg concludes from his experiments with tissue cultures of chicken embryos and liver, spleen and vascular tissue of rabbit embryos with the addition of 5 per cent lithiocarmine solution that the histiocytes and monocytes are phylogenetically older than the lymphocytes and granulocytes. A transformation of macrophages into lymphocytes or granulocytes was never observed.

W. C. HUEPER.

THE PIGMENTED STRIAE OF THE VISCERAL PLEURA. F. ORSÓS, *Verhandl. d. Deutsche path. Gesellsch.* **23**:495, 1928.

The pigmented striae of the visceral pleura correspond in their location to the intercostal spaces. The primary cause of this local increase of pigment depends on the relatively lower tension of the pleural and subpleural tissue in the region of the intercostal spaces. The circulation of the lymph, blood and air is decreased in these areas. The striae are only distinct in the region of the upper lobes due to the concentrated tension of the diaphragm in the apical part and the minor respiratory movements of the upper lobes. Pigmented striae on the lower lobes are present in emphysema because the diaphragm is immobile.

W. C. HUEPER.

REACTION OF THE VESSEL WALL IN ARTERIOSCLEROSIS. M. SCHMIDTMANN and M. HÜTTICH, *Virchows Arch. f. path. Anat.* **267**:601, 1928.

Feeding rabbits with cholesterol led to differing results in the individual animals: In some the blood pressure rose, in others it remained the same. Cholesterol, and other colloidal substances, increased the sensitiveness of the animals to the pressor action of epinephrine. With preparations of excised arterial wall, it could be shown that the reaction of the tissue was of great importance in determining the sensitizing activity of cholesterol: The activity was marked in acid mediums, but entirely lost in alkaline mediums. It could also be shown that the ground



substance of young arteries is alkaline, while a progressive change toward the acid side takes place with age. Young growing rabbits did not respond to cholesterol feeding with increase in blood pressure, while in adult animals both increase in blood pressure and arteriosclerotic changes took place. According to these results, the cause for the difference in response to cholesterol between young and old animals appeared to be the physicochemical constitution of the vessel wall, especially the reaction of the ground substance. It is, of course, admitted that other factors enter into the predisposition of age for arteriosclerosis.

B. R. LOVETT.

DEVELOPMENT OF ATHEROSCLEROSIS. H. BEITZKE, *Virchows Arch. f. path. Anat.* **267**:625, 1928.

The author presents evidence, chiefly on a histologic basis, for the theory that local injury to the media is the primary event in the development of arteriosclerosis, and that the thickening and degenerative change of the intima is secondary to this. It is an exaggeration of the process which occurs physiologically in old age: As the media wears out, the intima becomes thickened. The finding of round patches of thickened intima, overlying weak points in the media, is evidence for this view. Calcification of muscle fibers in the media have been found from the twentieth year on, and over some of these places sclerotic patches develop. The most significant change, however, is tearing and degeneration of the elastic tissue, or, in muscular arteries, degeneration of the muscular fibers, so that the arterial wall bulges. These defects are compensated for by growth of the intima. One other type of early arteriosclerotic change, found only in the aorta, is cellular infiltration and scarring around the nutrient arteries, resembling syphilitic aortitis. There is a tendency for calcium and cholesterol to be deposited in the patches of thickened intima, but the author denies that this is the primary change. He attributes the fatty plaques in the aorta of young people to tearing of the intima during a sudden rise in blood pressure, and regards this lesion as entirely distinct from atherosclerosis.

B. R. LOVETT.

ANATOMIC CHANGES IN THE KIDNEYS OF INFANTS. L. SCHWARZ, *Virchows Arch. f. path. Anat.* **267**:654, 1928.

Histologic examination of the kidneys of infants revealed inflammatory and infiltrative changes regularly associated with pneumonias. These were similar to the changes described by Schridde and Councilmann in scarlet fever, and consisted of progressive stages: round cell collections in the capillaries, interstitial infiltration of lymphocytes or of plasma cells, and finally connective tissue scars. They occurred in infants dying in the fourth week of life or later, at which time pyuria also was most frequently observed. Inflammatory and infiltrative renal changes were rarely found under three weeks, and then were chiefly of lymphatic nature. They were frequently associated with disease in the mother. The glomerular changes described by Herxheimer were observed in 30 per cent of cases in the first three weeks, and in 100 per cent of infants over that age with inflammatory renal changes. Since in almost all instances adequate anatomic basis for the change was found, the view of Herxheimer that it is a congenital malformation could not be supported.

B. R. LOVETT.

LIPOID AND IRON DEPOSITION IN THE SUPRARENALS AND TESTES IN INFANCY. A. TOBECK, *Virchows Arch. f. path. Anat.* **267**:690, 1928.

The bodies of 100 infants under 1 year of age were examined for the lipoid and iron content of the suprarenals and testes. Lipoid was found chiefly in the cells of the inner zone of the suprarenal cortex, and the amount appeared to be markedly influenced by the presence of disease. Thus it was increased in acute inflammations, and reduced in chronic septic processes. Iron, present in the

reconstruction zone of the cortex from the fifth week on, increased until the fifth month and then decreased until the end of the year. Its presence was attributed to hyperemia and slight hemorrhages during growth of the cortex.

In the testes, lipoids were found constantly in the interstitial cells without relation to disease, but the presence of lipoid in the germ cells, found only occasionally, appeared to be pathologic. Iron was present in the interstitial cells from the eighth day on. No relationship could be demonstrated between the suprarenals and testes with regard to lipoid and iron metabolism.

B. R. LOVETT.

FORMATION OF TRUE STONES IN THE SMALL INTESTINE. H. BARTH, Virchows Arch. f. path. Anat. **267**:716, 1928.

True enteroliths, composed largely of inorganic material, are usually found only in the large intestine. In the case here described, eleven true stones were found at autopsy in a pouch of the ileum, which had apparently arisen following an operation for carcinoma of the sigmoid twenty years previously. The stones were faceted, and consisted of 80 per cent inorganic material, mostly calcium salts, around a core of feces.

B. R. LOVETT.

PEPTIC ULCER OF THE STOMACH AND DUODENUM IN THE DOG. K. HOSOMI, Virchows Arch. f. path. Anat. **267**:726, 1928.

In fifteen cases of plastic operation on the common bile duct in dogs, erosions of the stomach and duodenum were produced in seven, and in four ulcers of the duodenum with erosions and hemorrhages in the stomach. Since narrowing or occlusion of the duct was invariably present, the cause of the ulcers was thought to be in part the disturbance in flow of bile. Other factors suggested were adhesions of the duodenum, inflammation of the bile passages, postoperative infection and trauma. The author regards peptic ulcer as a local disease, and not as a manifestation of general disease.

B. R. LOVETT.

TABETIC ARTHROPATHY. A. R. MORITZ, Virchows Arch. f. path. Anat. **267**:746, 1928.

Moritz made an exhaustive histologic study of the knee joints of a woman dying with tabes and syphilitic aortitis. There was marked arthritis of both knees, with genu varum and subluxation on the left side, and genu valgum on the right. Macroscopically, the cartilage, where exposed to excessive strain, appeared white, rough and bulging from proliferative and degenerative changes. Where the pressure was least, the cartilage was normal or atrophic. The condyles of the femurs and tibiae showed thickening of the spongiosa, with cartilaginous adhesions obliterating the intercondyloid fossae. Exostoses were numerous on the left side, but not on the right.

The chief microscopic changes in the cartilage were proliferation of the cells with increase in volume of the ground substance. More advanced changes consisted of mucoid degeneration of the ground substance, with farther growth of the cell columns, as in preparation for enchondral ossification. Signs of atrophy from disuse were evident in places relieved from pressure. Here the cartilage was surrounded by a fibrous covering, and was itself partly fibrocartilage. Enchondral ossification, following the proliferative changes and altering the shape of the joint, played a prominent rôle in the arthritic process. Cartilage-covered exostoses were found arising not only from the cartilaginous joint surfaces but also from the periosteal surfaces. Evidence of wear and tear on the joint surfaces was a prominent feature, with necrosis of the fibrous or cartilaginous coverings, and replacement by a dark red fibrinous substance. Results of trauma were also seen: tears followed by callus formation. Intra-articular fracture, an important occurrence in the tabetic joint, was probably responsible for marked shortening of the lateral condyle of one femur. New bone formation had taken place at the

insertions of the ligaments, and especially over the condyles of the tibiae. Here the process had given rise to new joint surfaces, shaped to meet the functional demands. Study of a second case in a less advanced state revealed that this new bone was probably periosteal callus, due to loosening of the intact periosteum from the bone. Pieces of old cartilage embedded in the new bone indicated that slight breaks had occurred previously.

B. R. LOVETT.

INVOLUTION AND REGENERATION OF THE THYMUS UNDER THE INFLUENCE OF BENZENE. J. E. LEWIN, *Virchows Arch. f. path. Anat.* **268**:1, 1928.

The ingestion of benzene leads to atrophy of the thymus in the rabbit, the picture of "accidental involution." There are two stages: the formation of an inverted gland and the period of connective tissue development with atrophy of lobules. The first period is characterized by a rapid lymphocytic disintegration and activity of the reticulo-endothelial cells. The latter cells hypertrophy, become isolated and form free macrophages, hemocytoblasts which in turn develop into pseudo-eosinophils, premyelocytes and myelocytes. In the second period besides an overgrowth of interlobular connective tissue there is formed a close-meshed network of collagen bundles within the lobules. The reticular cells play a prominent rôle in the formation of new lymphocytes, a lesser rôle by the adventitial cells. The regeneration of the thymus is accompanied temporarily by myelo- and erythropoiesis, most pronounced in the cortex.

V. C. JACOBSEN.

COMPLETE NECROSIS OF THE WANDERING SPLEEN WITH COMPENSATORY PERIPHERAL NODULAR HYPERPLASIA OF SPLENIC TISSUE. J. CATSARAS, *Virchows Arch. f. path. Anat.* **268**:181, 1928.

Obstruction of the main splenic artery of the misplaced spleen is the cause of necrosis of the greater portion of the organ, while the peripheral parts receiving their blood supply from the capsule remain alive. These living fragments are supported by a more or less favored collateral circulation and undergo a consequent hypertrophy, producing a striking multinodular distortion of the organ.

V. C. JACOBSEN.

HISTOLOGIC CHANGES IN ENDOCARDITIS LENTA. T. ISTAMANOWA, *Virchows Arch. f. path. Anat.* **268**:224, 1928.

Thirty cases of endocarditis lenta, in which the histologic changes were not very specific, were studied. There were two main types: a rapid, acute form with toxins affecting liver and a lymphocytotoxin acting on spleen and lymph nodes. The tendency to embolism accounts for most of the fatalities in this group. The frequent focal nephritis is due to bacterial emboli. There is a sharp reaction of the reticulo-endothelial apparatus which, however, does not involve the whole vascular system. A second type more chronic and milder, is without gross visceral changes. There is progressive weakness of the heart and hyperemia of the internal organs, hyperplasia of the reticulo-endothelial cells such as occurs in many other infections, with a transformation of lymphocytes into plasma cells.

V. C. JACOBSEN.

BONE SARCOMA ARISING IN A CASE OF OSTITIS DEFORMANS (PAGET). A. VON ALBERTINI, *Virchows Arch. f. path. Anat.* **268**:259, 1928.

The case of a woman, aged 51, who had had typical Paget's disease for at least five years is reported. The pelvic girdle, left femur and tibia were most affected. Spontaneous fracture occurred and revealed a sarcoma arising in the fibrous marrow with tendency to osteogenic type in femur and tibia. The tumor in the shaft was of polymorphocellular type. At death, metastases were found in the lungs, liver and kidneys, and tumor thrombus in the left iliac vein. The ques-

tion of traumatic etiology was discussed, but the author believes great care should be used in assigning importance to trauma.

V. C. JACOBSEN.

**BILATERAL CHROMAFFIN TUMORS OF SUPRARENALS WITH HYPERTENSION.**  
KURT SCHRÖDER, *Virchows Arch. f. path. Anat.* **268**:291, 1928.

A woman, aged 42, with hypertension and diabetes, at autopsy showed bilateral chromaffin suprarenal tumors, hypertrophy of the heart, atherosclerosis of the large and medium vessels and atrophy of the pancreas. The hypertension, vessel changes and hypertrophy of heart were regarded as due to excessive suprarenal secretion by the tumors, because of the strongly positive Vulpian iron chloride reaction of the tumors. The vessel changes were those of ordinary atherosclerosis.

V. C. JACOBSEN.

**THE MORPHOLOGY OF EXPERIMENTAL HYPERTHYROIDISM PRODUCED BY SYSTEMIC FEEDING WITH THYROID SUBSTANCE.** E. KLIWANSKAJA-KROLL, *Virchows Arch. f. path. Anat.* **268**:374, 1928.

Feeding young rats with thyroid substance in the first ten to twenty days produces slight adrenal changes. In thirty days there is a hypertrophy of adrenal cortex. The longer the feeding period, the more prominent the increase in size of the adrenal glands. The change is confined largely to the cortex, and is due to an increase in fatty material within the cells. This accumulation of fat in the cortex is the result of an infiltration from the blood which showed a hyperlipemia.

V. C. JACOBSEN.

**A RARE FORM OF FULMINATING GLOMERULO-NEPHRITIS.** R. HÜCKEL, *Virchows Arch. f. path. Anat.* **268**:395, 1928.

A report is given of a case of acute nephritis in a woman, aged 53, which was fatal in two and one-half days. The histologic picture is of a toxic focal glomerulo-nephritis due to hemolytic streptococcus infection. The focal lesions present are regarded as not embolic. The toxin attacks the first part of the glomerular capillary at the dilated end of the afferent artery, with thrombus formation and destruction of endothelium, and to some extent the walls of the afferent arteries. In some respects, it resembles a diffuse nephritis. Mixed types occur, but greatest importance is given to the factor producing the focal lesion.

V. C. JACOBSEN.

**THE RÔLE PLAYED BY THE LUNG, LIVER AND SPLEEN IN FAT AND LIPOID METABOLISM.** G. L. DERMAN and SAMUEL LEITES, *Virchows Arch. f. path. Anat.* **268**:440, 1929.

Following the ingestion and intravenous injection of oleic acid into dogs, the fatty acid mixed with neutral fat and lipoid can be demonstrated in the lungs, liver and spleen. Oral administration of olive oil led to its deposit in the alveolar epithelium of the lung, liver cells, Kupffer cells and the reticulo-endothelium of the spleen. Split products are also present in liver and spleen, while after lienectomy or ligation of the splenic vessels split products can still be demonstrated in the lung. Following ingestion of a solution of cholesterol in olive oil by mouth, cholesterol and its esters can be found in the lung, liver and spleen. Intravenous injection of this cholesterol solution is not followed by its accumulation in the lung and liver; only a mixture of neutral fat and fatty acids can be observed. Oral and intravenous feeding of lecithin results in no accumulation of lecithin in the lungs, liver or spleen. Histochemically, only neutral fat and fatty acids can be shown. The authors conclude that the lungs, liver and spleen play an active rôle in fat and lipoid metabolism, and that the metabolites may be built up into other fats and lipoids. There is an endogenous as well as exogenous fat and lipoid infiltration of the organs.

V. C. JACOBSEN.

THE PATHOLOGIC ANATOMY OF PLUMBISM. HELEN FREIFELD, *Virchows Arch. f. path. Anat.* **268**:456, 1928.

The changes in the meninges are slight, the greatest damage being in the brain substance where there are many foci of phagocytic cells about nerve cells and fibers. There is proliferation of the endothelium of the capillaries. The earliest change noted is a metachromasia of Nissl's granules. Possibly an alkalization of the tissues occurs. In the cerebellum are changes in the Purkinje cells as well as in the vessels. Gliosis is present in the anterior horns of the spinal cord which is postulated as being due to alterations of metabolism of the sympathetic nervous system, the products of metabolism accumulating in the perineural and endoneural cells leading to connective tissue proliferation. Nerve fibers are irritated to cause colic. There is formation of Renautis bodies by connective tissue overgrowth in the nerve sheaths, and analogous changes occur in the ganglion cells of the ganglion solare. In the spinal nerve roots, Gombalt's periaxial neuritis and proliferation of Schwann's cells are found. The arteries of the spinal cord and the kidney show Heubner's type of intimal proliferation. Innervational disturbances of the vessels cause the vascular changes. In the bone-marrow there is a proliferation and then a flood of megakaryocytes into the circulation of the obstructing lung capillaries. The anemia is hemolytic, but only small amounts of iron are deposited in the spleen and the bone-marrow and none in the liver. Hyperplasia of the reticulo-endothelial cells in the internal lymph nodes is caused by lead albuminate passing from the intestine to the nodes.

V. C. JACOBSEN.

MALFORMATIONS OF EXTRAHEPATIC BILE DUCTS. FRIEDRICH FEYRTER, *Virchows Arch. f. path. Anat.* **271**:20, 1929.

The author reviews and groups the reports available in the literature; he adds three original observations. Cystic dilatation and atresia may be found together; the malformations are generally multiple. The teratologic termination point is early. The causes are unknown.

ALFRED PLAUT.

A PECULIAR FORM OF SYSTEMIC BONE-MARROW DISEASE COMBINED WITH OSTEOSCLEROSIS. A. A. WASSILJEFF, *Virchows Arch. f. path. Anat.* **271**:134, 1929.

A man, aged 30, had pain in the legs for five years, severe anemia and thrombopenia. At autopsy, diffuse osteosclerosis, pachymeningitis hemorrhagica interna and subserous hemorrhages were found. The bone-marrow, which was gray and pink, was full of bone lamellae. Most of it was supplanted by large honey-combed cells with one small nucleus; they were from ten to fifteen times larger than a lymphocyte. The blood vessels in the periosteum and in the bone marrow contained heaps of such cells; similar cells were found in the lymph nodes and lungs. The reticulum and endothelium in the lymph nodes were hyperplastic. The ground substance of the protoplasm of the large cells took no stain. This disease cannot be classified with any known systemic disease; it obviously is no tumor.

ALFRED PLAUT.

ANATOMY OF GAUCHER'S DISEASE IN INFANTS. H. HAMPERL, *Virchows Arch. f. path. Anat.* **271**:147, 1929.

In addition to the usual localizations (spleen, liver, lymph nodes and bone-marrow), Gaucher cells were found in the cortex of the thymus, tonsils, adenoids, lymph follicles of the intestine, zona reticularis of the suprarenal gland, and perhaps the lung. Kerasin and cerebrosin constituted 3 per cent of the dry substance of the spleen. The lipoids, phosphorus and total cholesterol were high, similar to the figures in Niemann-Pick's disease. The presence of Gaucher cells in the other organs is due to the special behavior of connective tissue and reticulum in the first year of life.

ALFRED PLAUT.

BAMBERGER-MARIE'S DISEASE. T. KONSCHIEGG, *Virchows Arch. f. path. Anat.* **271**:164, 1929.

The histologic description is given of bone lesions in a man, aged 56, who had typical hypertrophic secondary pulmonary osteo-arthritis. Sarcoma of vertebrae was the underlying disease.

ALFRED PLAUT.

THE MORPHOLOGIC CHANGES IN BLOOD AND HEMATOPOIETIC ORGANS UNDER THE INFLUENCE OF BENZENE AND ITS DERIVATIVES. A. WORONOW, *Virchows Arch. f. path. Anat.* **271**:173, 1929.

Rabbits withstood subcutaneous injections of xylene for several weeks, and after initial leukopenia, had leukocytosis up to 30,000. Since xylene is as good a fat solvent as benzene, one cannot explain the action of benzene by its fat-solving power. Phenol, even in high doses, proved innocuous. Considering the  $\text{CH}_3$  groups of xylene important, the author injected other methylated phenols like toluol, cumol and cymol, with one and three  $\text{CH}_3$  groups, respectively. They acted like xylene. Some of the pathologic forms of leukocytes were similar to those found in myelogenous leukemia. The author hopes that in varying such experiments one may succeed in producing myelogenous leukemia.

ALFRED PLAUT.

SPLEEN LESIONS IN MALARIA. B. A. PIOTOTAKIS, *Virchows Arch. f. path. Anat.* **271**:194, 1929.

In hyperacute malaria with death during the first attack, the enlarged spleen is chocolate-colored, grayish black or deep black; it is pulpy and may flow in the pan. Such colors of spleen are not found in any other infectious disease; they are characteristic of malaria, in the peracute form. In such spleens the reticulum shows no reaction; there is only hyperplasia of the endothelium. In acute malaria, the reticulum reacts; in chronic malaria, the connective tissue does also.

ALFRED PLAUT.

PARTICIPATION OF BOWMAN'S CAPSULE IN DIFFUSE GLOMERULONEPHRITIS. EDMUND RANDEATH, *Virchows Arch. f. path. Anat.* **271**:197, 1929.

A network of fine capillaries surrounds the glomerulus; it is connected with the intertubular capillaries. Accumulations of leukocytes in such periglomerular capillaries are found together with circumscribed swelling of the adjoining parietal layer of the capsule; over this swelling the lining cells desquamate. Although micro-organisms, pneumococci, for instance, were found in capillaries nearby (autopsy immediately after death), the lesions are not to be explained as directly due to bacterial influence. The mesenchyme of the capsule must have become permeable, and that leads to the changes in the glomerular epithelium. Spindle-shaped oxydasepositive cells were found in the Bowman's capsule. The hyaline thickenings of the capsule in older cases may be later stages of the described lesion. Randerath considers the term "glomerular epithelium" misleading; he speaks about "glomerulothel" in analogy to Maximow's mesothel.

ALFRED PLAUT.

LYMPHOGANULOMATOSIS, PARTICULARLY ITS PULMONARY FORM. A. BERNSTEIN, *Ztschr. f. Tuberk.* **52**:202, 1928.

A case of lymphogranulomatosis with exclusive localization in the lungs is reported with detailed clinical and necropsy data.

MAX PINNER.

CARCINOID OF THE SMALL INTESTINE AND APPENDIX. BJARNE DAHL, *Norsk Mag. f. Laegevidensk.* **90**:233, 1929.

Three cases are described: In one the tumor was benign and of extremely slow growth; in the other two cases large glandular metastases gave rise to

mechanical disturbances, but here also the microscopic sections showed a benign nature of the growth with regular cells, no mitoses and no inflammatory reaction in the surrounding tissues. The relatively benign nature of carcinoid and its metastases is emphasized.

EXPERIMENTAL INVESTIGATIONS OF HEMATOGENOUS STAPHYLOCOCCAL NEPHRITIS. MARTTI HÄMÄLÄINEN, Arb. a. d. path. Inst. d. Univ. Helsingfors 5:271, 1929.

Human hematogenous staphylococcal nephritis occurs in two main morphologic forms, which pathogenetically also represent two groups: mycotic eliminative nephritis and emboli suppuration nephritis. These two types were reproduced experimentally in rabbits. Leaving out of consideration typical embolic staphylococcal nephritis, the author includes the other kind in the same pathogenetic group as due to capillary metastasis. This group takes in all cases due to elimination of staphylococci and also those of the embolic-suppuration type in which many foci develop in the kidney, especially in the cortex. Mixed forms may occur.

PHIL SHAPIRO.

THE GENESIS OF ACUTE VALVULAR ENDOCARDITIS. OSTEN HOLSTI, Arb. a. d. path. Inst. d. Univ. Helsingfors 5:401, 1928.

The frequent discrepancy between obvious clinical signs and negligibly slight gross postmortem observations led the author to investigate histologically the entire leaflets in cases of valvular heart disease. He took complete sections from all four valves and their roots. He found that inflammatory changes were much more frequent than one would suspect from gross examination. In twenty-eight cases of ulcerous, verrucous and syphilitic endocarditis there was a valvulitis in 66, or 59 per cent, of the 112 valves. In a control group of 64 cases there were changes in 49, or 19 per cent, of the 256 valves, and these were only slight. The right valves were more frequently affected than the left, and the auriculoventricular more than the semilunars. Rarely is the valvulitis only superficial (12 per cent). A localized defect in the endothelium is followed by a reactive process in the sub-endothelium. The valvulitis is often only deep (41 per cent) and the gross changes so slight that without histologic examination they would go undetected. Vascularization begins at the root of the valve, is preceded by exudation and is followed by fibroblastic proliferation. It proceeds toward the periphery. This is more common in the right side of the heart than in the left. Combined deep and superficial valvulitis is most common. It may represent two independent processes, with or without fusion; a deep valvulitis may extend to the endothelium, or a superficial valvulitis may burrow backward to the root of the valve. The deep lesions, detectable often only by microscopic examination, may clarify the incongruities that arise between clinical murmurs and inadequate gross observations at autopsy.

PHIL SHAPIRO.

NORMAL AND MORBID HISTOLOGY OF THE VESSELS IN THE MUCOSA OF THE NOSE AND MAXILLARY ANTRUM WITH SPECIAL REFERENCE TO ATROPHIC RHINITIS. ARNO SAXÉN, Arb. a. d. path. Inst. d. Univ. Helsingfors 5:733, 1928.

Fundamentally, the atrophy in ozena is not nutritive. Circulatory disturbances are not the primary cause of the atrophy but they may act as secondary factors. The changes in the vessels involve especially the veins and capillaries in the erectile tissue, while the arterial changes are of less importance.

PHIL SHAPIRO.

### Microbiology and Parasitology

THE BACTERIOLOGY OF MASTOIDITIS IN INFANTS. MARY B. SPAHR, Am. J. Dis. Child. 37:541, 1929.

Cultures from the middle ear of an infant are valueless as indications of the causative organism in an accompanying mastoiditis. Infants suffering from otitis

media and showing the constitutional symptoms of vomiting, diarrhea and failure to gain in weight often have infected mastoid antrums. In all cases in which intestinal organisms (*B. coli-communior* or bacillus or Morgan) were found on culture from the mastoids, the prominent clinical symptom was diarrhea, accompanied in some instances by vomiting. Pneumococci, streptococci and staphylococci were also frequently found in cultures from the mastoids of infants. These organisms did not give rise to a characteristic symptomatology.

AUTHOR'S SUMMARY.

THE RELATION OF THE TONSILS TO ACUTE RHEUMATISM DURING CHILDHOOD.  
ALBERT D. KAISER, Am. J. Dis. Child. **37**:559, 1929.

An analysis of 439 cases of rheumatism in children discloses the following facts: The most susceptible age for the first attack of rheumatism was between 8 and 14 years. Nearly twice as many first attacks of rheumatism developed in children whose tonsils were still present. Recurrent attacks occurred 10 per cent less often in children who had had their tonsils removed after the first attack than in those whose tonsils had not been removed. The incidence of carditis as a complication in acute rheumatism was nearly as frequent in children who had undergone a tonsillectomy as in those who had not. Chorea occurred as a complication in acute rheumatism with equal frequency in children operated on and not operated on, but the association of carditis with chorea was less frequent in children whose tonsils had been removed. Tonsils are the avenue of infection in many cases of rheumatism and bear a definite relationship to this disease. Their removal should be advocated for the rheumatic and the potentially rheumatic child, until more is known of the etiology of rheumatism.

AUTHOR'S SUMMARY.

EXPERIMENTAL WHOOPING COUGH. LOUIS W. SAUER and LEONORA HAMBRECHT, Am. J. Dis. Child. **37**:732, 1929.

The injection of *B. pertussis* (Bordet-Gengou) into the larynx of five healthy young monkeys was followed, after a period of incubation of from one to three weeks, by spontaneous, paroxysmal coughs. Similar coughs followed inoculation in the nares of three healthy young monkeys. The total and differential white cell counts usually showed the transient lymphocytosis characteristic of pertussis in human beings. The bacillus was recovered from deep throat cultures; also from the larynx, trachea and lungs after death. The bacillus was recovered during the height of the cough from an animal that had been inoculated with the bacillus recovered, in turn, from the lung of another coughing animal. Animals that recovered were immune to subsequent injections of various strains of *B. pertussis*.

AUTHORS' SUMMARY.

PSEUDOMEMBRANOUS ENTEROCOLITIS AND MASTOIDITIS ASSOCIATED WITH AN INFECTION WITH MORGAN'S BACILLUS. T. LEONARD SUTTON, Am. J. Dis. Child. **37**:814, 1929.

A case of pseudomembranous enterocolitis is presented in which the clinical evidences of infection of the middle ear developed later, and in which Morgan's bacillus was isolated from the heart blood and from the middle ear.

AUTHOR'S SUMMARY.

STUDIES ON FILTRABLE VIRUSES (VACCINE VIRUS). ROBERT N. NYE and FREDERIC PARKER, JR., Am. J. Path. **5**:147, 1929.

Further experiments are described demonstrating the multiplication of vaccine virus in tissue cultures. Vaccine virus could not be cultivated using killed tissues or under anaerobic conditions. The virus when suspended in Locke's solution, was destroyed if heated to 55 C. for twenty minutes or to 37.5 C. for twenty-four hours. The optimum hydrogen ion concentration for survival of the virus in



glycerin was found to be  $p_H$  7. After centrifugalization, the bottom layer contained more virus than the top layer. The virus could not be filtered through a Mandler filter. Experiments on the viricidal action of hyperimmune calf serum are described.

#### AUTHORS' SUMMARY.

#### THE OCCURRENCE OF TUBERCULOID REACTION IN THE INGUINAL GLANDS IN EARLY SYPHILIS. H. E. MICHELSON, Arch. Dermat. & Syph. 19:66, 1929.

The histologic character of the inguinal nodes in early syphilis is variable, two distinct lesions being observed. One is a subacute proliferative and exudative inflammation, which may be termed nonspecific lymphadenitis; the other is a tuberculoid reaction which histologically is indistinguishable from that found in tuberculous adenitis. The inguinal nodes from twenty-nine persons with early untreated syphilis were excised and examined microscopically. Nonspecific inflammation occurred in twenty-one and tuberculoid reactions in eight. Tuberculoid structures were found much earlier in the inguinal nodes than in cutaneous lesions. If the tuberculoid reaction is a manifestation of high resistance, then probably the production of immunity or antibodies begins early in the lymphatic system.

#### AUTHOR'S SUMMARY.

#### BACTERIA IN THE TONSILS. L. M. ROLVOGT and S. J. CROWE, J. A. M. A. 92:962, 1929.

The tonsils and adenoids were removed at operation in 100 patients with a history of acute attacks of tonsillitis. After washing in 70 per cent alcohol, the tonsils were ground in sand and cultures were made. The hemolytic streptococcus was the predominating organism grown in 91 per cent and the staphylococcus in 8 per cent. In one case no growth was obtained. There is no apparent connection between the predominating type of organism found in the tonsils and the clinical symptoms. The majority of these cultures were made during the winter months, and all were made between November, 1927, and April, 1928. More than 50 per cent of the patients from whose tonsils a hemolytic streptococcus was grown in pure culture were children under 11 years of age. The majority of those in whom a staphylococcus was the predominating organism were over 25 years of age. The average time between the last acute attack of tonsillitis and the tonsillectomy was one month. In eighty-one cases the hemolytic streptococcus was the predominating organism in both the tonsils and the adenoids. In eight there was a heavy growth of staphylococcus from both the tonsils and the adenoids. In ten there was a heavy growth of staphylococcus from the adenoid culture and a pure culture of streptococcus from the tonsils. A culture made by swabbing the surface of the tonsil is a reliable index of the predominating organism in the crypts.

#### AUTHORS' SUMMARY.

#### INFESTATION WITH DIPHYLLOBOTRIUM LATUM, FISH TAPEWORM, WITH ESPECIAL REFERENCE TO NATIVE CASES. MOSES BARRON, J. A. M. A. 92:1587, 1929.

Native infestation with the fish tapeworm is rapidly increasing in the United States and Canada. There appear to be three endemic areas established thus far: the lakes of the northern peninsula of Michigan, the lakes in the northern part of Minnesota and the lakes around Winnipeg in Canada. The complete life cycle of the parasite has been carefully worked out in America, as well as in Europe. Two intermediate hosts and one definitive host are the means through which the life cycle is completed. Infestation in man can occur only through the ingestion of raw or insufficiently cooked fish. A large proportion of the population of Finland is infested because of the consumption of raw fish. Of the cases of native infestation, the larger percentage occur in Jewish women and children who have tasted the raw minced fish in the preparation of gefüllte

fish. Infestation of fish occurs not only through their ingestion of infested crustaceans but also through the ingestion of other fish that are infested. Pernicious anemia does not occur any more often through infestation with the fish tapeworm than through infestation with the beef tapeworm and the incidence is slight. The removal of the tapeworm apparently does not alter the course of the anemia, nor does the presence of the tapeworm modify the profoundly beneficial effect of the feeding of liver in bringing back the blood picture practically to normal. Thus far, nineteen authentic cases of native infestation have been reported, three of which were added here. Undoubtedly, there could be included many other cases of patients who, though not born in America, obviously were infested after coming to this country.

AUTHOR'S SUMMARY.

TULAREMIA IN MINNESOTA. E. C. HANSON and R. G. GREEN, J. A. M. A. **92**:1920, 1929.

Cases of tularemia in Minnesota are reported. In one case the infection followed the bite of a wood tick (*Derma-cento variabilis*), and in another it followed the bite of a finger by a cat.

CHRONIC MENINGOCOCCEMIA. W. R. GRAVES, A. D. DULANEY and I. D. MICHELSON, J. A. M. A. **92**:1923, 1929.

A case of chronic meningococcemia is described. Meningococcus infection is classified as (1) acute meningococcemia, fulminating or followed by meningitis and (2) subacute or chronic meningococcemia, with or without metastasis. A table of thirteen cases of prolonged meningococcemia reported in this country is included.

DISSOCIATION OF *B. ANTHRACIS*. W. J. NUNGESTLER, J. Infect. Dis. **44**:73, 1929.

A laboratory stock culture of *B. anthracis* aged under various culture conditions yielded six additional culture types. These forms have all been reisolated from the usual anthrax colony type, "purified" by over 100 serial single colony isolations. After similar purification all variants were caused to revert to the usual colony type. The form giving rise to the usual rough, gray colony has been designated as the R form. One variant formed small smooth raised colonies which were termed the S form. All forms were studied according to colony characteristics, morphology, variations in different mediums, and dissociation under different conditions in cultures and in vivo. The virulence was tested in mice and guinea-pigs; all variants when first isolated from the R form could produce death. R forms derived from avirulent forms were not virulent. R forms derived from slightly virulent forms had an increased virulence approximating that of the original R form.

FROM AUTHOR'S SUMMARY.

THE ACTION OF BACTERIA ON FAT. ROY H. TURNER, J. Infect. Dis. **44**:126 and 134, 1929.

1. Five groups of differential plating mediums for lipase-producing bacteria have been compared for sharpness of differentiation, sensitivity, inhibition of bacterial growth, and tendency to give false positive reactions.

Those mediums which depended on gross disintegration of tallow or globules of cottonseed oil emulsion for differentiation were found to lack sharpness of differentiation, to be low in sensitivity, but did not inhibit growth of organisms studied and gave no false positive reactions. The development of clear zones may be greatly facilitated by using fats made up of short chain fatty acids or by adding bile to the medium.

Those mediums which depend on hydrogen ion indicators for differentiation were found lacking in sensitivity due probably to the little effect which the higher fatty acids have on  $pH$ , and they gave false positive reactions in the presence of fermentable carbohydrates.

The Nile blue sulphate medium gave remarkable sharpness of differentiation and high degree of sensitivity, but inhibited the growth of certain organisms. The meaning and mechanism of fading zones is discussed; they do not seem to indicate the formation of lipase. Whether Nile blue sulphate acts as a differential stain or as an indicator is discussed.

2. The action of a strain of lipolytic bacteria on the globules of an emulsion of cottonseed oil in a thin layer of agar medium containing Nile blue sulphate has been observed with the microscope and photomicrographs made. To aid in explaining the observations on cottonseed oil, a similar study has been made of pure fats and combinations of two or more. What has been seen to happen to cottonseed oil is set forth with interpretations as follows:

A globule of oil, well removed from a bacterial colony, becomes blue, due to the staining of unsaturated fatty acids, oleic and linoleic, split by diffusible lipase. Part of the fatty acids are converted into soaps. There is diffusion into the agar surrounding the globule of blue staining material, probably mixtures of these same fatty acids and their soluble soaps. If near the colony, this material quickly becomes decolorized and disappears; if further away, this happens slowly. Marked shrinkage of the globule occurs; it usually takes a crescentic shape. This shape seems to be the result of surface activity of the remaining lipid material, which no longer completely fills the cavity in the agar. Shrinkage of some globules is accompanied by protrusion of a bundle of crystals. These are crystals of the solid fatty acids, linoleic and palmitic, or their derivatives. Crystals are seen to form in the agar well removed from visible globules of oil. It is suggested that these are derived from lipid material which existed in solution or colloidal suspension.

The method of study is of greatest value when used in conjunction with accurate quantitative methods.

AUTHOR'S SUMMARY.

#### A COMPARISON OF SEVEN STRAINS OF ORGANISMS CAUSING HUMAN BLASTOMYCOSIS. DOROTHY SPRING, J. Infect. Dis. 44:169, 1929.

Different strains of organisms causing human blastomycosis, even within the Gilchrist group, differ materially; morphologically in test tube and hanging-drop cultures; in fermentation of sugars and resistance to certain dyes, and in virulence. Yeast cells in pus are sensitive to dyes to the same extent as those in culture. They resist heat at 48 C. for twenty minutes; so it appears that heat therapy does not promise success. Similarly, dye therapy does not rest on a scientific basis. Generalization of infection in laboratory animals occurs rarely except in mice. The mouse is the animal of choice for diagnostic tests, and it is difficult for the organism to gain a foothold at all in rabbits and to a less extent in guinea-pigs.

AUTHOR'S SUMMARY.

#### TABARDILLO, AN AMERICAN VARIETY OF TYPHUS. H. MOOSER, J. Infect. Dis. 44:186, 1929.

Tabardillo is a distinct variety of typhus fever which can be differentiated from European typhus by inoculation in guinea-pigs. The disease observed in the southern United States is identical with tabardillo of Mexico and is distinct from Brill's disease observed in New York which belongs to the European variety.

AUTHOR'S SUMMARY.

#### SPONTANEOUS TUBERCULOSIS IN SNAKES. JOSEPH D. ARONSON, J. Infect. Dis. 44:215, 1929.

Tubercles were found in the various organs of four garter snakes (*Thamnophis sirtalis*) found dead in the Philadelphia Zoological Garden. Large numbers of acidfast but not alcoholfast bacilli were observed within them. The tubercles consisted of a central area of necrosis surrounded by cells with a large, clear, vesicular nucleus, by connective tissue, and by some deeply staining smaller cells,

with numerous eosinophils scattered throughout. From the lesions was isolated an acidfast but not alcoholfast chromogenic bacillus that grows best from 20 to 25 C. and is pathogenic for garter snakes, frogs, goldfish, chameleons and red lizards, but not for guinea-pigs, rabbits, chickens or pigeons. The bacillus differs in cultural and antigenic character and in staining reaction from previously described pathogenic poikilothermic acidfast bacilli. The name *Mycobacterium thamnophicos* is suggested for this organism.

AUTHOR'S SUMMARY.

TWO OUTBREAKS OF FOOD POISONING PROBABLY DUE TO *B. CLOACAE*. ENOS B. BUCHANAN and EMERSON MEGRAIL, J. Infect. Dis. 44:235, 1929.

An organism of the cloacae type was present, and organisms of the paratyphoid group were absent, in two outbreaks of food poisoning. The cultures of this organism obtained from the food produced a substance toxic for rabbits. From the epidemiologic and experimental data reported, it is probable that *B. cloacae* was the cause of these outbreaks.

AUTHORS' SUMMARY.

EPIZOOTIC LYMPHADENITIS IN GUINEA-PIGS. EMERSON MEGRAIL and ROBERT N. HOYT, J. Infect. Dis. 44:243, 1929.

A small outbreak of epizootic lymphadenitis in guinea-pigs was shown to be due to  $\beta$  and  $\gamma$  types of streptococcus. *Staphylococcus albus* was also present, probably as a secondary invader. The source of the infection could not be ascertained. Experimental production of the disease was apparently through the skin.

AUTHORS' SUMMARY.

PRODUCTION OF COLDS WITH *MICROCOCCUS CATARRHALIS*. JOHN E. WALKER, J. Infect. Dis. 44:254, 1929.

Two of three intranasal inoculations with *M. catarrhalis* in the same person were followed by typical colds. The inoculated organism was recovered on culture. In one instance the inoculated organism was not found on early culture, but was present later when the exudate became more mucoid. The experiments, taken in conjunction with two previous acute infections of the upper respiratory tract associated with *B. influenzae* and *B. bronchisepticus*, are believed to indicate that the bacteria cultivated from the nasal exudate are the primary cause of colds.

AUTHOR'S SUMMARY.

THE MORPHOLOGY OF *COCCIDIOIDES IMMITIS*. FLORENCE E. AHLFELDT, J. Infect. Dis. 44:277, 1929.

A short historical sketch of the life cycle of *Coccidioides immitis* is given. A hanging block preparation showed that it took from about seven to ten days for the mycelium to form into spherical or almost spherical spores. Tissues stained by the osmic acid method of Murray showed many interesting details. Some structures took the osmic acid stain and some took the contrasting stain. For convenience we called these types osmic-acid-positive and osmic-acid-negative. In some preparations we found that these two forms were contained in the same shell. This type had a large double-contoured membrane taking the contrasting stain, and the membrane was frequently spiculated and ruptured. Within this membrane were the osmic-acid-positive and osmic-acid-negative forms, which frequently were passing through the ruptured double-contoured membrane. Such structures as these suggest a bisexual life. In the previous report we noted that it took ten days for the animals to manifest any clinical symptoms. During the present morphologic study it was found that ten days was required for spore formation. Thus it would seem that it is the dissemination of the spores that is coincident with the spread of disease.

AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF CERTAIN REACTIONS INDUCED BY "RESTING BACTERIA."  
ARTHUR ISAAC KENDALL and MITZUTERU ISHIKAWA, J. Infect. Dis. **44**:282, 1929.

The reduction of methylene blue by "resting bacteria" in the presence of certain carbohydrates is precisely paralleled by the fermentation of these same carbohydrates in cultural mediums inoculated with identical strains of proliferating bacteria. It is inferred that resting bacteria, therefore, initiate changes in substrates which they, as proliferating bacteria, would subsequently use for their energy requirements. The initial changes thus induced in substrates are not associated with the proliferation of the organisms; they occur under conditions of time, temperature and environment which preclude growth. The substrate, thus initially altered, is conceived of as in a state peculiarly adapted to rapid utilization for energy. The high degree of specificity of this preliminary change in various carbohydrates resides in the hereditary chemical architecture of the microbial protoplasm. It seems to be manifested at the surface of the microbe. The reactions induced by "resting bacteria" will not ordinarily supplant cultural reactions; the technic is more complex and cumbersome.

AUTHORS' SUMMARY.

FATAL SEPTICEMIA IN MAN DUE TO BACILLUS (SALMONELLA) SUIPESTIFER.  
JOHN T. BAUER and MARGARET MCCLINTOCK, J. Infect. Dis. **44**:292, 1929.

A fatal human infection suggesting typhoid fever and due to an organism with the cultural and serologic characteristics of *B. suipestifer* is described. The source of the infection remains undetermined.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF POSTMORTEM BACTERIOLOGIC EXAMINATION WITH  
SPECIAL REFERENCE TO STREPTOCOCCI AND ENTEROCOCCI. EMANUEL Z.  
EPSTEIN and M. A. KUGEL, J. Infect. Dis. **44**:327, 1929.

In these bacteriologic investigations at necropsy in the sixty-six blood cultures and sixty-two bone marrow cultures, at least one organism was always present. In forty-two heart muscle cultures, five were sterile, and in forty-three valve examinations four were sterile. Streptococci of all kinds were isolated in 79 per cent of the cultures of the blood, in 67 per cent of the bone marrow, in 47 per cent of the heart muscle and in 40 per cent of the normal valves. Nonhemolytic streptococci were found in blood, bone marrow, heart muscle or valve in 86 per cent of the cases. The infrequency of the pneumococcus, *streptococcus beta* and anaerobic organisms was observed. A strikingly high percentage of nonhemolytic streptococci tested were identified as enterococci. It seems that no significance can be attached to the recovery at necropsy of such organisms as *Streptococcus alpha*, *Streptococcus gamma*, enterococcus, *Staphylococcus aureus*, *Bacillus coli* and *Bacillus pyocyaneus* unless the same organism has been found during life.

AUTHORS' SUMMARY.

THE OCCURRENCE OF BACTERIUM TULARENSE IN THE WOOD TICK, DERMACENTOR OCCIDENTALIS, IN CALIFORNIA. R. R. PARKER, C. S. BROOKS and  
HADLEIGH MARSH, Pub. Health Rep. **44**:1299, 1929.

The recent occurrence in San Benito County, Calif., of an unrecognized pathologic condition in cattle heavily infested with ticks has resulted in the demonstration in adults of a natural tularemia infection due to the Pacific coast tick, *Dermacentor occidentalis* Newmann. This observation is of importance, because this tick, which is common in many sections of California and in southwestern Oregon, is a frequent parasite of man, and, hence, an apparent potential source of human tularemia. It has also been reported in horses, cattle, deer, dogs, sheep and rabbits. The data at hand are not sufficient to justify an assumption as to what part *B. tularensis* might have played in the pathologic involvement of the affected cattle. They are of interest chiefly as further evidence of the wide dissemination of tularemia in nature and of the numerous avenues for human contact.

THE OXIDATION BY BACTERIA OF COMPOUNDS OF THE PARAPHENYLENDIAMINE SERIES. S. ELLINGWORTH, J. W. M'LEOD and J. GORDON, J. Path. & Bact. **32**:173, 1929.

The oxidations of the various methyl substitution products of paraphenylenediamine hydrochloride which may be produced by chemical oxidizing agents resemble closely those produced by certain bacteria. The facility with which such diamines are oxidized to colored products is increased as the number of methyl groups in the molecule is increased, and for this reason the tetramethyl compound is the most delicate reagent for indicating the oxidizing activities of bacteria. In the absence of free access of oxygen the various diamines appear to have a roughly similar toxicity for bacteria. When oxygen has free access to bacterial colonies previously exposed for a few seconds to a solution of a diamine, it is found that the monomethyl compound is the most toxic, and the tetramethyl the least toxic, and the variation in toxicity is closely associated with the speed with which the colonies develop a black tint. The tetramethyl compound, which differs from the other diamines examined in not developing a black tint on oxidation, and which is less toxic on oxidation than the others, is the most suitable for use in diagnostic bacteriology. It should be used in a 0.5 per cent solution, which is the lowest concentration giving frank color reactions in bacterial colonies. The bacterial colonies capable of oxidizing the tetramethyl derivative to a blue-violet also reduce this compound, so that the color fades away again, although at varying speeds with different bacteria and most slowly in the case of those which oxidize it most rapidly. In the case of the other compounds oxidized in bacterial colonies to a black tint, the oxidizing colonies are picked out permanently, since the development of the black color coincides with the death of the bacteria, and there cannot therefore be any subsequent reduction. The tetramethyl compound indicates the oxidizing activity of a number of bacteria not picked out by the other diamines, notably *B. pertussis* and *B. influenzae*, of which the former is the most active. All attempts to prepare mediums containing paraphenylenediamines or modifications of such substances, on which actively oxidizing bacteria would develop colored colonies as they grow, have failed.

AUTHORS' SUMMARY.

THE EFFECT OF CERTAIN FACTORS ON THE GROWTH OF THE PNEUMOCOCCUS. HEDLEY D. WRIGHT, J. Path. & Bact. **32**:203, 1929.

For full growth of the pneumococcus a small amount of fermentable carbohydrate (dextrose) is necessary (0.2 per cent). Excess leads to production of high acidity and so hastens autolysis. Thermostable nitrogenous substances are adequately supplied by 1 per cent peptone; relatively thermolabile constituents, essential to growth, are to be found in yeast extract and blood in large amount, in extract and in serum in small amounts, and also in peptone. Heating organic fluids, especially peptone, serum and yeast extract, causes them to become inhibitory to the growth of the pneumococcus. This inhibitory effect is diminished or its development is prevented by conditions favorable to reduction. The pneumococcus is also inhibited by excess of salts and readily destroyed by salts in the absence of colloids. Under certain conditions small quantities of calcium salts are favorable to growth. From a study of growth curves it is concluded that the length of the period of lag and the rate of growth depend on all the nitrogenous constituents of the medium and not solely on the so-called accessory factors.

AUTHOR'S SUMMARY.

THE EFFECT OF GROWING SMOOTH AND ROUGH CULTURES IN SERUM. J. A. ARKWRIGHT and R. M. PITT, J. Path. & Bact. **32**:229, 1929.

In nutrient broth diluted 1 in 5 with distilled water and in normal rabbit serum diluted 1 in 5, little effect in turning S cultures into R was detected even in old cultures. Culture mediums containing serum with somatic agglutinins for the S strain growing in them have a strong tendency to turn the S culture into the R

form, in the course of one or two weeks. This property is independent of the presence of flagellar agglutinins, and is exhibited whether the S somatic agglutinins have been produced by the organism in the culture (*B. typhosus*) or by another (*B. enteritidis*, Gaertner), so long as these agglutinins agglutinate the bacterium in the culture. The effect of an agglutinating serum on the production of the R form from the S form is not seen if the S somatic agglutinins have been removed by heating at 70 C. or by specific absorption with the appropriate bacterial emulsion. Neither growth in R serum nor growth in normal serum with or without a steamed S emulsion had the effect of transforming R into S cultures. Cultures with R somatic agglutinin which formed S looking colonies and were not agglutinated by salt solution appeared in several old cultures, especially those which had been definitely R at some time; since these were R antigenically they should be regarded as essentially R. All the cultures were still motile at the end of the various experiments, though in several instances they had been growing in anti-flagellar serums.

· AUTHORS' SUMMARY.

TRYPSINIZED SERUM TELLURITE COPPER SULPHATE AGAR FOR THE ISOLATION OF *CORYNEBACTERIUM DIPHTHERIAE*. V. D. ALLISON and T. H. AYLING, *J. Path. & Bact.* **32**:299, 1929.

The addition of 0.05 per cent of copper sulphate to trypsinized serum tellurite agar increases its value in the isolation of *C. diphtheriae* from nasal, throat and ear swabs. The action of the medium is as follows: The growth of staphylococci and streptococci is prevented; *C. diphtheriae*, *C. hofmannii* and organisms of the diphtheroid group grow out unrestricted, and are much more readily recognizable in cultures. The spread of organisms of the *B. proteus* type, so often present in swabs from the ear, is inhibited. The differential appearance of colonies of *C. diphtheriae*, *C. hofmannii*, *C. xerosis* and other organisms of the diphtheroid group is more accentuated on this medium than on trypsinized serum tellurite agar. Cultures of *C. diphtheriae* on the medium produce a characteristic somewhat pungent odor. A series of swabs from acute cases of diphtheria was inoculated on to plates of the copper sulphate medium for the isolation of *C. diphtheriae*; the swabs were also inoculated on to slopes of Löffler's medium for the microscopic examination of stained films from the resultant cultures, owing to the atypical appearance microscopically of some strains of *C. diphtheriae* when grown on the copper sulphate medium. By this means it has been shown that the presence or absence of virulent *C. diphtheriae* may be reported within forty-eight hours from the receipt of the swab. Growth on the copper sulphate medium has no effect on the virulence of *C. diphtheriae*.

AUTHORS' SUMMARY.

HYDATID INFESTATION (*ECHINOCOCCUS GRANULOSUS*) IN SHEEP, OXEN AND PIGS, WITH SPECIAL REFERENCE TO DAUGHTER CYST FORMATION. N. HAMILTON FAIRLEY and R. J. WRIGHT-SMITH, *J. Path. & Bact.* **32**:309, 1929.

The distribution and incidence of degeneration in 6,497 sheep cysts, in 929 ox cysts and in 727 pig cysts are considered. Forty-three examples of early endogenous daughter cyst formation were studied in these hosts. Degeneration or rupture of the parent cyst was never observed, and the adventitia was normal in thirty-nine instances. The frequent incidence of degeneration noted in old mother cysts of large dimensions is essentially a secondary phenomenon due to increased intracystic tension occasioned by the growth of young endogenous daughter cysts. The present study constitutes the only series of observations dealing with the early stages of endogenous daughter cyst formation and the results are incompatible with the view that they originate under conditions menacing the life of the parasite. One hundred and sixty-two examples of exogenous daughter cyst formation were studied. The mother cyst was degenerated and ruptured in eighty (49.4 per cent). The adventitia was normal in 129 (79.6 per cent), sclerosed and thickened in 27

(16.6 per cent), and calcified in 6 (3.7 per cent). Exogenous cyst formation was found to be entirely independent of the adventitia. Such cysts are formed by a localized evagination of both layers of the mother cyst with constriction and fusion at the neck of the protrusion, and subsequent separation into the pericystic space. Three stages in the evolution of exogenous cysts are described, and the high incidence of degeneration of the original mother cyst is shown to depend on its mechanical separation from the adventitia by daughter cysts which as a result of local pressure produce the tessellation effects discussed in the text. The presence of intracuticular vesicles (pseudodaughter cysts) was described and specially studied in pig cysts where they were found to originate as hyaline degenerations of the laminated layer. Their presence was also observed in other hosts including man. In our opinion nonrecognition of the true nature of the intracuticular vesicle constitutes the basis on which the whole classic theory of the intracuticular origin of the daughter cyst has been founded. Cuticularization of the brood capsule as described by Dévé is confirmed. Our observations also support the main thesis of Dévé that the vesicular evolution of the scolex constitutes the most common and important source of endogenous daughter cyst formation.

AUTHORS' SUMMARY.

ON SEASONAL VARIATIONS IN BONY WEIGHT IN PULMONARY TUBERCULOSIS.  
M. KESAVA PAI, *Tubercle* 10:212, 1929.

There seems to be a general agreement of weight curves in all parts of the world, the apparent differences being due to differences in climate between the localities where the observations are made. Extremes of heat and cold and dryness of the air cause a fall of weight, while a pleasant temperature like that of summer in colder countries and the cold season in the tropics produces a rise in the weight curve. Rains have no particular effect on body weight. The factors discussed in this paper have an important bearing on the location of sanatoriums in India. These should not be constructed in the plains, where the climate is hot, nor on the west coast, where it is both hot and moist. Also, too dry a climate may not be congenial. A moderate elevation with a cool summer and moist cooling winds during the hotter months is desirable.

H. J. CORPER.

CO-RELATION OF CALCIUM METABOLISM, PARATHYROID FUNCTION AND  
CHRONIC PULMONARY TUBERCULOSIS. PHILIP ELLMAN, *Tubercle* 10:257,  
1929.

The calcium content of the blood serum in pulmonary tuberculosis varies only within normal limits (from 9 to 12 mg. per hundred cubic centimeters). In cases responding favorably to treatment, the calcium content can be increased, but only within normal maximal limits. The administration of calcium or parathyroid must be continued over prolonged periods, if calcium retention is to be promoted. A combination of parathyroid extract with calcium lactate has proved as effective as any. Microscopic examination of the parathyroid glands in cases of pulmonary tuberculosis shows signs of increased functional activity. It is concluded that there is a definite relationship between pulmonary tuberculosis, on the one hand, and calcium metabolism and parathyroid function, on the other.

H. J. CORPER.

THE EARLY INFILTRATION AND ITS RELATION TO THE DEVELOPMENT OF  
PHTHISIS. H. V. MORLOCK, *Tubercle* 10:267, 1929.

The development of phthisis from an apical lesion is uncommon. The "early infiltration" is described and particular emphasis placed on the acute commencement of the disease and the possibility of mistaken diagnosis at this stage. The early infiltration may be a transient condition, healing to leave only a scar, which may later be discovered and considered to be the early manifestation of the disease,



but which, in fact, is the end-result of an attack of pulmonary tuberculosis. The "early infiltration" is often progressive, and when it has advanced, the condition of the lungs is then indistinguishable from phthisis.

H. J. CORPER.

LIVING TUBERCLE BACILLI IN A SEPTIC TANK EFFLUENT. S. LYLE CUMMINS and C. M. ACLAND, *Tubercle* **10**:310, 1929.

Living tubercle bacilli were found in the effluent from a septic tank, indicating the ability of these organisms to resist the digestive processes of this procedure.

H. J. CORPER.

INFLAMMATIONS OF THE PLACENTA AND FETAL SEPSIS. FRIEDRICH WOHLWILL and HANS ERIHARD BOCK, *Arch. f. Gynäk.* **135**:271, 1929.

Four cases of diffuse placentitis are described. The bacteria were *Bacillus coli* in two cases; streptococci in one case; and a mixed infection of gram-negative bacilli (*B. coli*) and gram-positive anaerobic bacilli in the fourth case. The pregnancies concerned were in the fourth and fifth month. The placentitis is regarded as secondary to fetal bacteremia. The organisms were distributed in large quantities in the placenta, especially the villous vessels which contained emboli of bacteria; other fetal organs as the liver, spleen and brain also contained large numbers of bacteria. The organisms in the villi had invaded the intervillous spaces through a break in the syncytial lining and thus infected the maternal blood stream. One mother died of sepsis which was considered secondary to the fetal septicemia, and another mother whose uterus was removed showed that the organisms had extended into the vessels of the broad ligaments. In the two other cases there were no or slight reactions in the maternal organism despite the diffuse distribution of bacteria in fetuses. One of these had an external thoracic defect which probably permitted direct entrance of organisms from the infected amniotic water. The case of streptococcal fetal infection was considered to be secondary to a maternal focus. The other cases are thought to have been infected through the amniotic water, and the latter was thought to have been infected secondary to criminal interference with pregnancy. The reactions of the fetus and its ability to cope with infection are discussed. The placenta showed an accumulation of countless leukocytes about the villi, chorionic plate and about the amnion. There were regressive and progressive changes and phagocytosis. Despite the overwhelming distribution of bacteria in many of the other fetal organs, no reaction was visible except in the liver about the vessels containing the organisms. There was also some accumulation of histiocytes. In a note mention is made of five more cases of fetal bacteremia occurring in fetuses of three to five months. Bacteria were found in the bronchi and gastro-intestinal tract of one fetus of only three months' development, showing that even in this early state infected amniotic water can be aspirated or swallowed.

A. J. KOBAC.

RETICULO-ENDOTHELIAL SYSTEM IN LEPROSY. H. G. RIECKE, *Beitr. z. path. Anat. u. z. allg. Path.* **80**:201, 1928.

The rarity of leprosy in Germany prompted the author to study and report a fatal case in a woman, aged 28. The lesions of the skin were of the tuberculous type; tissue obtained from them during life was studied. Numerous nodular lesions were present in the mucous membranes of the nose, mouth and pharynx, and the larynx was diffusely involved. The liver and the spleen contained the characteristic nodules. The spleen revealed myeloid transformation of the pulp, and many lepra cells. The lymph nodes were hyperplastic and contained large reticulo-endothelial cells filled with lipoid material. The lepra cells, whenever present, were of the same size and morphology as the reticulo-endothelial cells and were filled with bacilli, but contained little or no lipoid. The storage of lipoid by the reticulo-endothelial cells is considered evidence of an abnormal lipoid metabolism in leprosy.

O. T. SCHULTZ.

ETIOLOGY OF INGUINAL GRANULOMA. A. MUSGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:257, 1928.

From local tissue removed by biopsy and from pus, in a case of inguinal granuloma, Musger isolated a pseudodiphtheriod bacillus, which he obtained also from the blood of the patient. A similar organism was later obtained from the blood and inguinal nodes of a second patient. When inoculated locally in guinea-pigs, the organism caused changes in the inguinal lymph nodes similar to those in the nodes in man.

O. T. SCHULTZ.

THE PATHOLOGY OF ACUTE DISSEMINATED MILIARY TUBERCULOSIS OF THE LUNGS. W. GRETHMANN, Beitr. z. Klin. d. Tuberk. **71**:1, 1928.

The microscopic structure of miliary tubercles is largely dependent on the degree of immunity. Neither the clinical observation nor the histologic criteria can definitely establish the duration of the disease. Vascular foci are found in not more than from 70 to 80 per cent of the cases. They may rupture into the blood stream. The tubercles in the intima contain usually not many tubercle bacilli. Their significance as sources of the dissemination is doubtful. The pathogenesis of miliary tuberculosis is still obscure. The author protests against Huebschmann's theory that all miliary tubercles start with a miliary caseous pneumonia, and may then show productive changes. The miliary tubercle develops in the blood vessel wall, and residues of the latter are usually found in its center. Most of the tubercle bacilli are found where nuclear debris is seen. The alveolar epithelial cells play an important rôle in the formation of the tubercle; they are transformed into epithelioid cells. This paper contains many good illustrations and complete clinical and pathologic data.

MAX PINNER.

TUBERCLE BACILLI IN HEN'S EGGS. RAEBIGER, Beitr. z. Klin. d. Tuberk. **71**:209, 1929.

Three chickens were infected with avian tubercle bacilli. Three days after the infection tubercle bacilli could be isolated in pure culture from the blood stream. Twelve eggs which were laid from ten to fourteen days after the infection were examined microscopically and culturally for the presence of tubercle bacilli. Fifty-two other eggs laid between the seventeenth and sixtieth day following the infection were examined only microscopically. The earliest date at which tubercle bacilli could be demonstrated in eggs was ten days after the infection. In all of the first twelve eggs tubercle bacilli could be demonstrated either microscopically or culturally. Out of the fifty-two eggs which were examined only microscopically, in nineteen or 36.5 per cent, tubercle bacilli could be demonstrated. Artificially infected eggs were boiled, and it was ascertained that avian tubercle bacilli may survive a five minute boiling period.

MAX PINNER.

EXPERIMENTS ON THE PRODUCTION OF TUBERCLES AND TUBERCULOID STRUCTURES IN THE SKIN OF HEALTHY PIGS FOLLOWING THE INJECTION OF LIPOIDS. A. HAIM, Beitr. z. Klin. d. Tuberk. **71**:269, 1929.

This is a complete report on extensive experiments which cannot be reported briefly. The main conclusions are that under certain conditions tubercle bacillus lipoids may produce typical tubercles in the skin of pigs. Other lipoidal materials and certain colloidal materials may produce similar lesions. Striking individual differences were observed.

MAX PINNER.

SPONTANEOUS TUBERCULOSIS IN MONKEYS. H. H. KALBFLEISCH and A. NOHLEN, Beitr. z. Klin. d. Tuberk. **71**:336, 1929.

This study was undertaken in order to establish the possible sources of error in experimental tuberculosis with monkeys. Both from their own experiments and

from an extensive review of the available literature, the authors conclude that monkeys living wild under normal conditions never contract tuberculosis. The frequency of tuberculosis in monkeys living in captivity depends on many different factors such as, crowding, uncleanliness, possible sources of infection, the amount of air currents, etc. Monkeys living in captivity are undoubtedly susceptible to tuberculosis, particularly if coresidence with an infected animal exists. The diagnosis of tuberculosis during the life time of monkeys can be done by clinical and roentgenologic observation. The roentgenologic data are important and reliable. Strictly extrapulmonary lesions occur only rarely, if ever. Tuberculin tests are unreliable, since tuberculous monkeys do not react essentially differently from normal monkeys. It was found that by keeping monkeys in the open air, even during cold periods in the moderate climate of Germany, the danger of infection was much decreased as compared with monkeys kept in stables. Spontaneous infection can be completely avoided if monkeys are kept in the open air and if all possible sources of infection, particularly infected animals are excluded.

MAX PINNER.

### Immunology

THE AVIAN, HUMAN, AND BOVINE TUBERCULIN REACTIONS IN CHILDREN.  
B. M. GASUL, *Arch. Pediat.* **46**:67, 1929.

The conclusions are that 110 children with pulmonary tuberculosis, all of whom reacted positively to the human and bovine tuberculin, failed to react to the avian tuberculin with the usual Pirquet test. No appreciable differences were noted in the reactions to the human and bovine types. The avian tuberculin appears to be specific only to tuberculosis caused by the avian type of tubercle bacillus.

AUTHOR'S SUMMARY.

THE PRECIPITABLE SUBSTANCES OF BACILLI OF THE SALMONELLA GROUP.  
J. FURTH and K. LANDSTEINER, *J. Exper. Med.* **49**:727, 1929.

Specific precipitable substances rich in carbohydrates, containing little protein and small amounts of a material apparently of fatty nature, have been prepared from the main serologic types of the typhoid-paratyphoid groups. The preparations in their present state of purity do not exhibit pronounced chemical differences in spite of serologic dissimilarity. In this respect the results differ from those observed with the polysaccharides of pneumococci. The specificity of the precipitin reactions of these substances parallels, in a general way, the so-called small flaking agglutination. Attempts to separate different fractions from the active substance serologically by means of precipitation with antibody solutions were, on the whole, unsuccessful. The differences in resistance to the action of acid and alkali were found to be characteristic for various specific carbohydrates.

AUTHORS' SUMMARY.

THE MECHANISM OF OPSONIN AND BACTERIOTROPIN ACTION. STUART MUDD, BALDUIN LUCKÉ, MORTON MCCUTCHEON, MAX STRUMIA and EMILY B. H. MUDD, *J. Exper. Med.* **49**:779, 797 and 815, 1929.

1. Methods are described for investigating the relation between phagocytosis of bacteria by polymorphonuclear leukocytes and certain physicochemical properties of the bacterial surface. Serum sensitization causes the following changes in the properties of acid-fast bacteria: increased cohesiveness, decrease in surface electric potential difference, decrease in the power of the bacteria to become wet by oil and increased phagocytosis. Tests have been conducted periodically with the serums of four rabbits under active immunization, with as many strains of acid-

fast bacteria; the parallelism between the alteration in bacterial surface properties and the promotion of phagocytosis by these serums have been, within the experimental error, complete. The percentage of phagocytosis of a given bacterial suspension has been found to depend both on the sensitizing serum component or components deposited on the bacterium and on the intrinsic properties of the unsensitized bacterial surface.

2. The combination of a substance or substances present in fresh immune rabbit serum, heated or unheated, or in fresh unheated normal rabbit serum, with a substance or substances in the bacterial surface, causes an increase in cohesiveness, a decrease in surface potential difference and a characteristic alteration in wetting properties of the bacteria, and prepares the bacteria for phagocytosis. The effective substance or substances in the serum may become so altered as the result of heating or aging that combination with the bacterial surface, while causing changes in bacterial surface properties indistinguishable by the present physicochemical tests from these just mentioned, may not lead to phagocytosis, or may lead to phagocytosis with a prezone not paralleled by a prezone in the changes in surface properties. Sensitization of bacteria with human serums causes changes in surface properties similar to those caused by rabbit serums, but does not lead to phagocytosis by rabbit leukocytes. The spreading requirements of rabbit polymorphonuclear leukocytes are evidently highly selective.

3. Rabbits infected intravenously with virulent mammalian tubercle bacilli have, in a majority of cases, developed circulating antibodies to a slight but appreciable degree. The increase in titer was detected in one group of rabbits within the second or third week, and in others during the second month, of infection. In rabbits with residual pulmonary foci, resulting from infection six months or more previously with human tubercle bacilli, on reinfection with bovine tubercle bacilli circulating antibodies developed promptly, strikingly in excess of those found during the course of primary infection. Such antibodies were present six or seven days after reinfection. The changes in titer during tuberculous infection, as detected by the bacterial surface reactions and by phagocytosis, were again, within the experimental error, in quantitative correspondence. The loss of the phagocytosis-promoting power in heated normal serum involves an exception to this correspondence between surface and phagocytosis effects. This exception was discussed in an earlier paper.

#### AUTHORS' SUMMARY.

THE INFLUENCE OF CHEMICAL AND OTHER AGENTS UPON THE TOXICITY AND ANTIGENIC POWER OF RICIN. EMMETT B. CARMICHAEL, *J. Pharmacol. & Exper. Therap.* **35**:193 and 223, 1929.

The preparation of several specimens of ricin is described. These exhibited such characteristic properties as coagulation by heat, toxicity when injected into animals and agglutination of mammalian blood corpuscles. The toxicity of ricin was destroyed by such oxidizing agents as potassium permanganate, 30 per cent hydrogen peroxide, ozone, chlorine, bromine and iodine. Ultraviolet light, particularly that with wave lengths between 225 and 250 millimicrons, was found effective in destroying the toxicity of ricin. Ricin detoxified by boiling or by partial oxidation with potassium permanganate retains its antigenic activity, so that serums of rabbits and guinea-pigs receiving injections of detoxified ricin protect white mice from fatal doses of untreated ricin. Prolonged treatment of ricin with a large excess of potassium permanganate destroys its antigenic power as well as its toxicity. A single large dose of ricin detoxified with potassium permanganate develops an immunity in rabbits strong enough to protect them from as many as 120 lethal doses of the untreated ricin. Serums from these rabbits in amounts as small as 0.25 cc. protect white mice against fatal doses of ricin. The antigenic activity of ricin is thus found to be less susceptible to oxidizing agents, such as potassium permanganate, than is its toxicity.

ARTHUR G. COLE.

IMMUNITY TO TUBERCULOUS SUPERINFECTION. BRUNO LANGE, *Ztschr. f. Hyg. u. Infektionskrankh.* **110**:185, 1929.

After carefully weighing all available evidence, Lange comes to the following conclusions: The experimental experiences and the observations in man show, beyond doubt, that a specific immunity develops in the course of active tuberculosis. The Behring-Römer doctrine of the acquired immunity of adults due to childhood infection is not sufficiently supported by experimental, epidemiologic or other evidence. In order to obtain a better judgment of the action of superinfection in man, additional experiments are necessary which approximate, as much as possible, the conditions existing in primary infection and superinfection in man. So far as the primary infection is concerned, this means the artificial production of an active infection which remains latent for a long time and tends to heal. In the case of superinfection, attention should be paid to the conditions normally present, such as infection with minimal doses and the variations of natural susceptibility which are so important in the course of the disease. A proper experimental investigation of the effect of the complex factors which lower resistance seems to be possible only when by additional experiments one is more thoroughly informed of the exact modification of an infection by a preceding one under conditions which exclude these complicating factors.

W. OPHÜLS.

## Tumors

MULTIPLE SUPERFICIAL BENIGN EPITHELIOMA OF THE SKIN. F. WISE, *Arch. Dermat. & Syph.* **19**:1, 1929.

The disease designated by Little as erythematoid benign epithelioma, in 1923, has for many years been recognized in this country as multiple, benign, superficial epithelioma of the skin. The lesions are usually basocellular new growths, arising primarily on unchanged skin; they may also be prickle cell lesions or mixed growths. Lesions of this kind have been confused with Bowen's disease, extramammary Paget's disease and (more rarely) arsenical epitheliomas and keratodermas. In microscopic preparations, Bowen's disease is a distinct entity with histologic features peculiar to itself and like any intra-epidermic carcinoma. The exact status of extramammary Paget's disease is still undetermined both clinically and histologically. Although the clinical diagnosis of multiple benign superficial epithelioma usually is not attended with many difficulties, the differentiation from Bowen's disease, extramammary Paget's disease, arsenical keratodermas and other lesions which closely simulate the multiple new growths is by microscopic examination of the lesions.

AUTHOR'S SUMMARY.

THE LYMPHOBLASTOMAS. H. L. KEIM, *Arch. Dermat. & Syph.* **19**:533, 1929.

The results in twenty patients with lymphoblastoma, including complete post-mortem studies in ten, are recorded. There is a striking variability of the clinical changes in this group of diseases, making proper classification extremely difficult. That seemingly widely divergent dermatoses are genetically related is established by the striking similarity of the microscopic picture. In each there are tumor cells of the lymphocyte series resting in a connective tissue reticulum, the distinguishing feature occurring in the degree of differentiation of the cells of the neoplasm. The term lymphoblastomas is given to the members of this group on the basis of their genetic relationship.

AUTHOR'S SUMMARY.

CANCER OF THE SKIN DUE TO OCCUPATION. W. J. O'DONOVAN, *Arch. Dermat. & Syph.* **19**:595, 1929.

The author cites the cases of eighteen patients with carcinoma who were in the tar industry, three in an anthracene factory, three with arsenic cancer of occupational origin, one oil carcinoma and one x-ray carcinoma. Sixty-one patients

with carcinoma of the hands are mentioned, and an effort is made to correlate the condition with the occupation of the patient.

A UNIFIED EXPLANATION FOR NEW GROWTHS ON MAN. HEINRICH MÜLLER, *Virchows Arch. f. path. Anat.* **269**:105, 1928.

A study of the literature, much thought and the results of careful study of many tumors, especially in relation to their growth and spread, led Müller to the following opinion: Carcinoma is regeneration gone wrong. Physiologic regeneration is stimulated either by the products of destruction of tissue or by a hormone coming from another organ. He points out that stimulation of new growths by hormones may occur, e. g., the growth of bones, hypertrophy of the breast during pregnancy, development of secondary sex characters, etc. These hormones, he argues, are specific. The tissue formation occurs through the mesenchyme tissues which are present throughout the entire body and which in part are in close relation to the vascular system. The replacement of tissues destroyed is overdone, but after proper replacement, it gradually regresses to the proper point. This replacement begins in the mesenchyme in long continued destruction or even in sudden destruction as by trauma and roentgen effect. Carcinoma may occur from increased regeneration which then continues as an independent regenerative process. This prolonged action is caused by a prolonged destruction of tissue manifestly due to insufficient blood supply. Histologic studies have shown that the capillaries concerned in regeneration (carcinoma) at first show an increase in size; finally, they are compressed by the epithelial cells and obstructed. The cellular damage leads to further release of hormones, which leads to further stimulation of growth. The formation of metastases occurs through hormones carried through the lymph and blood stream. It is easily understood why the lymph nodes in the line of drainage in a primary carcinoma should be involved since they receive the lymph containing the released hormones from the primary growth. The predilection of the liver may be explained by its slow blood stream rate and prolonged activity of hormones. The fact that in many cases there is a predilection of organ systems for the formation of metastases may be explained by the assumption of specific sensitivity of their mesenchyme to the oncoming organ hormones.

This point of view differs from most others in that it disregards the hypothetic changes in character of the carcinomatous cells and allows a physiologic interpretation. Naturally, in pathologic anatomy one sees things as they are, or rather were, when the tissues were removed, and the dynamics of the processes cannot be studied.

V. C. JACOBSON.

THE EFFECT OF DIET ON TUMOR GROWTH (EXPERIMENTS WITH RAT SARCOMA).

E. FRIEDBERGER and I. GRÜNSTEIN, *Ztschr. f. d. ges. exper. Med.* **62**:344, 1928.

Tumor growth is influenced by disturbances of nutrition in the sense that insufficient or deficient diet retards tumor growth. This is equally true when the quantity of food is insufficient and when the quality of food is at fault (vitamin deficiency through heating, insufficient quantity of mineral salts, etc.).

Conversely, excessive food favors tumor growth. The authors emphasize that the influence of diet on neoplastic growth was known to the ancients and in medieval times, but appears to have been forgotten in modern times. They give an extensive bibliography dealing with the clinical as well as the experimental phases of the subject.

BALDUIN LUCKE.

THE SIGNIFICANCE OF ATROPHY AND REGENERATION IN EXPERIMENTAL TAR CANCER. A. R. JONKHOFF, *Ztschr. f. Krebsforsch.* **26**:25, 1928.

Studies of the successive epithelial developments in the production of tar cancer in white mice gave the following stages: (1) periods of excessive growth of hair

alternating with intervals of absence of hair; (2) the appearance of papillomas in connection with growth of hair; (3) possible disappearance of these papillomas; (4) definite tumors, eventually becoming malignant, appearing only in the later stages of growth of hair, and (5) increasing atrophy and disappearance of hair and other accessory structures of the skin. Epithelial malignancy appears to be the sequel of associated atrophy and regeneration, and does not occur until the former has become pronounced.

H. E. EGGERS.

ROENTGEN CARCINOMAS IN MICE. A. R. JONKHOF, *Ztschr. f. Krebsforsch.* **26:32**, 1928.

Of six mice subjected to prolonged irradiation with the roentgen rays, tumors developed in four. In one the tumor was definitely carcinomatous; in the others it took the form of a carcinoma sarcomatoides, which, however, the writer regards as of truly epithelial derivation for the following reasons: Occasionally, the epithelial cells could be seen taking the spindle shape of those of the tumor; the tumor cells could be seen gradually blending into epithelial cells; in sites where tumor had not developed, there was cutaneous atrophy similar to that seen in the development of tar cancers, and in one of the animals there were pulmonary metastases which showed epithelial cornification. Long latent periods were observed in all the mice.

H. E. EGGERS.

SARCOMA OF THE PERICARDIUM. D. M. CHAJUTIN, *Ztschr. f. Krebsforsch.* **26:72**, 1928.

The writer reports a case of primary spindle cell sarcoma of the pericardium. In the literature he was able to collect only seven well established cases in addition to his own. Of the six reported cases in which the sex was given, only one was in a female. These tumors occurred predominantly at an early age.

H. E. EGGERS.

A CONNECTIVE TISSUE MIXED TUMOR OF THE FEMALE BREAST. S. KUROSU, *Ztschr. f. Krebsforsch.* **26:99**, 1928.

A detailed description is given of a mixed tumor of the breast, with a composition summarized by the following designation: fibrochondro-osteo-angiosarcoma. A number of similar cases have been reported previously—with sufficient frequency to warrant their designation as connective tissue mixed tumors of the breast. The author regards the various elements as resulting from metaplasia rather than from displacement.

H. E. EGGERS.

### Medicolegal Pathology

CARBON MONOXIDE AS A TISSUE POISON. J. B. S. HALDANE, *Biochem. J.* **21:1068**, 1927.

There have always been at least two explanations of the way carbon monoxide exerts its poisonous action, and for a long period one of them has maintained a definite supremacy in its general acceptance. This is the well known theory of anoxemia, that by reason of the great affinity of carbon monoxide for hemoglobin, the oxygen is replaced, and that all the subsequent chemical, functional, structural and other alterations which may follow in the wake of carbon monoxide poisoning owe their origin solely to this deprivation of oxygen. A vast amount of experimentation, much of it with physical chemistry applied to biology, has strongly supported this theory. The other theory, without minimizing the importance of anoxemia and the rôle played by hemoglobin, also advocates that CO is a direct tissue poison.

In spite of the little experimental proof that it has received, this last view has been resolutely defended by a few to whom the observations recorded in this

article by Haldane probably afford considerable relief. By the use of moths and seeds of water cress (*Lepidium sativum*), hemoglobin was excluded; rats were also used. All the results point to the ability of CO to lessen or inhibit oxidation by catalytic substances that unite with CO instead of O<sub>2</sub>. For example, a rat with presumably all its hemoglobin occupied by CO and kept alive by increasing the partial pressure of O<sub>2</sub> was quickly killed with more CO, but not with an inert gas such as N<sub>2</sub>.

Haldane suggests that tissues probably contain several catalysts with different affinities for CO and O<sub>2</sub> and exhibiting different behaviors with variations of the partial pressures of CO and O<sub>2</sub>. He also announces that CO in sufficiently strong concentrations, no matter how made, has an odor like garlic, and to one of his colleagues like tar. A number of procedures carried out to abolish the odor were unsuccessful. Usually CO is described as an odorless gas.

E. R. LE COUNT.

THE DANGER OF INTRAVENOUS ADMINISTRATION OF ELECTRARGOL. E. QUATER and B. LEWITIN, *Zentralbl. f. Gynäk.* **51**:2803, 1927.

After several intravenous injections of this colloidal solution into two patients with severe puerperal fever, symptoms regarded as anaphylaxis developed almost at once after another dose. There was difficulty in breathing, cyanosis, a rapid or undetectable pulse, a chill with severe shivering and other symptoms of profound shock. Both women finally recovered. One death has been observed. The authors succeeded in producing similar effects experimentally in one of two guinea-pigs, but only after a number of intracardiac injections.

E. R. LE COUNT.

DEATH FROM HEMORRHAGE AS A SEQUEL OF MISCARRIAGE. F. FEDERLIN, *Zentralbl. f. Gynäk.* **51**:3068, 1927.

Severe or fatal hemorrhage is said to follow designedly interrupted pregnancy more often than spontaneous miscarriage. Since Neu (Ist die Blutung beim Abort eine Indikation zur sofortigen Entleerung des Uterus, *München. med. Wchnschr.* **67**:1350, 1920) stated a few years ago that death from hemorrhage as a sequence of miscarriage was practically unknown, eighteen such deaths have been reported. To these, Federlin adds one, that of a married woman subject to metrorrhagia and to intermenstrual periods of from six to eight weeks. She therefore did not know she was about three months pregnant. She had bled so much that she was admitted to the hospital practically pulseless, and died in a few hours. Little influence on the laxness of the uterus was exerted by remedies that cause uterine contraction. The placenta and fetus lay loose in the uterus, and no bleeding took place when they were removed. No wound or other injury of the uterus or vagina was found after death.

E. R. LE COUNT.

GANGRENE OF THE LEGS FOLLOWING ABORTION. G. V. PÁLL, *Zentralbl. f. Gynäk.* **51**:3246, 1927.

This form of gangrene is due to bacterial arteritis and thrombosis of the femoral artery or of some of its divisions. The infection starts in the uterus. About sixty cases are reported, in which there were thirty deaths without amputation and eighteen recoveries after amputations in twenty-four patients. The woman cared for by Páll died about thirty-six hours after the entire right leg became gangrenous from an obturating clot high up in the femoral artery. Hemolytic streptococci were recovered from the blood during life. The abortion was criminal and at the third month of gestation.

E. R. LE COUNT.

POSTMORTEM EXAMINATIONS AND ACCIDENT INSURANCE. W. DI BIASI, *Aerztl. Sachverst.-Ztg.* **35**:27, 1929.

Five cases are mentioned briefly: (1) prostatic carcinoma with metastatic tumors in the bones and lymph glands demonstrated as the cause for a death which,



it was claimed, was the result of an injury of the chest followed by pulmonary tuberculosis; (2) necrosis of the hands, said to have resulted from freezing, which was found to have its cause in changes of the spinal cord due to anemia; (3) edema and passive hyperemia of the lungs from fibrous myocarditis and cardiac dilatation, which was confused during life with asthma from dust; (4) ascending renal infection from fractured pelvic bones and a torn urethra, disclosed by a post-mortem examination as the cause of death after liability had been denied; (5) a claim that a broken back and its sequels had caused death, which it was found had been caused by a primary cancer of the lung.

E. R. LE COUNT.

HEMORRHAGE AT THE BASE OF THE BRAIN FROM RUPTURED ANEURYSMS OF THE CEREBRAL ARTERIES. E PAWLOWSKI, *Aerztl. Sachverst.-Ztg.* 35:65, 1929.

Since the study of Charcot and Bouchard, almost a century ago, spontaneous intracerebral hemorrhage has been ascribed to rupture of miliary aneurysms of small arteries or arterioles due to sclerosis or patches of necrosis in the vessel walls. The arteriosclerosis is generalized and associated with nephritis, hypertension and hypertrophy of the heart, all developing in the middle or later decades of life. The aneurysms discussed by Pawlowski are altogether different. They

*Distribution of 397 Aneurysms of Large Intracranial Arteries*

Arteria fossae Sylvii . . . . .	92	Arteria cerebri posteriori . . . . .	14
Arteria basilaris . . . . .	83	Arteria cerebri anteriori . . . . .	10
Arteria carotidis interni . . . . .	60	Arteria meningea media . . . . .	5
Arteria communicans anterior . . . . .	42	Arteria cerebelli inferiori . . . . .	4
Arteria corporis callosi . . . . .	26	Arteria arachnoidea . . . . .	3
Arteria communicans posterior . . . . .	20	Arteria ophthalmica . . . . .	3
Arteria cerebri medii . . . . .	16	Arteria cerebri superioris . . . . .	2
Arteria vertebralis . . . . .	15	Multiple vessels . . . . .	1
Vessel anomaly . . . . .			

occur at all ages, and hypertension, arteriosclerosis, etc., do not accompany them with any constancy. Explanation of these aneurysms of the larger subdural or intraleptomeningeal arteries has been difficult. Mechanical factors connected with the arrangement of these vessels, the way they branch, absence of much support from adjacent structures, congenital anomalies in them and thinness of their walls have all been suggested; also that with any one or more of such factors actively concerned the relatively high blood pressure in the cerebral arteries and their short distance from the heart are important aids to the development of the aneurysms.

It is commonly held that syphilis is remotely concerned with their origin, or altogether without any influence. Some authorities favor trauma as the cause, and point out the many irregularities about the clinoid processes of the sphenoid bone, the elevations on the clivus, the way the vertebral and other arteries may be bruised by the edges or rims of bony openings or passages in which they course. To these are added the strain put on the vessels when the head is injured and the brain with the fluid in and about it is jolted back and forth, and the pull made on the vessels when the rounded contour at different places in the cranium is flattened or the cranial bones are broken.

Pawlowski refers to two investigations of conditions intimately related to the cause of these aneurysms. One of them was reported recently by Forbus (*Centralbl. f. allg. Path. u. path. Anat.* 44:243, 1929) and dealt with congenital defects in the muscular layers of arteries in many parts of the body. He found them in twenty-

five of thirty-one apparently normal cerebral arteries. Pawlowski believes aneurysms may easily form in such weakened places when they are bruised or slightly torn by muscular strains. The other (Reuterwall, O. P.: *Ueber bindegewebig geheilte Risse der Elastica interna der Arteria basilaris*, Stockholm, 1923), was a systematic examination of the large arteries at the base of the brain, which resulted in the finding of many scars resembling healed lacerations in their walls. These two researches are, in a way, complementary, since they possess a common end: weak regions in the vessels where saccular outpouching may readily occur. For three of the nine deaths which Pawlowski adds to others (397 in all) from rupture of such aneurysms, he obtained a history of injury. The frequency with which the aneurysms are located on certain arteries, according to the table accompanying his discussion, is slightly different from that found by Szekely (*Beitr. z. gerichtl. Med.* 8:162, 1928), whose summary is not included with those of several others in the table. The statistics of both authors comprise altogether 554 aneurysms, which means death from rupture of these aneurysms in 554 persons.

E. R. LE COUNT.

### Technical

THE SEDIMENTATION TEST IN PULMONARY TUBERCULOSIS. H. A. CLEGG, *Tubercle* 10:205, 1929.

The normal sedimentation rate by the Zeckwir and Goodel method, in which 2 cc. of 3 per cent sodium citrate and 8 cc. of blood in a 15 cc. centrifuge tube are used, was 9.6 cc. red cells at one hour. In the cases of normal sedimentation investigated, the physiologic variation was slight. The sedimentation rate in pulmonary tuberculosis appears to be an accurate measure of the activity of the lesion, and, as an additional clinical test, is of use in forming a diagnosis and prognosis. The test is of more use in prognosis than in diagnosis, and has not yet proved of value in early cases. Active cases investigated showed an abnormal rate of sedimentation. Several observers have found a normal sedimentation rate in active pulmonary tuberculosis, thus differing with the author and with Westergren whose observations were based on 72 and 340 cases, respectively. There is general agreement as to the utility of the test in relation to clinical observations.

H. J. CORPER.

CELLULOID PLATES FOR MOUNTING MUSEUM PREPARATIONS. H. MERKEL, *Centralbl. f. allg. Path. u. path. Anat.* 45:38, 1929.

Merkel favors celluloid plates instead of glass, especially for sections of the brain, because they can be cut easily with a knife or scissors in thicknesses up to 1.5 mm., are transparent, or can also be obtained in white or black to afford contrast, and can be easily perforated to permit the passage of retaining threads.

GEORGE RUKSTINAT.

POSTMORTEM EXAMINATION OF THE HEAD OF NEW-BORN. ERIK RYDBERG, *Acta path. et microbiol. Scandinav.* 6:145, 1929.

The bones of the cranial vault are carefully separated from the parietal dura, and removed piecemeal. The dura is then examined and removed sufficiently so that the brain can be taken out in the usual way, except that the brain-stem is cut across, so that the tentorium and the contents of the posterior fossae can be examined thoroughly. The advantages of the method are that extravasations of blood over the surface of the brain can be studied satisfactorily in situ without the admixture of blood set free during the opening of the skull; the veins that open into the longitudinal sinus can be followed easily; the tentorium can be examined in situ, and the brain removed without damage. The disadvantage of the method lies in the fact that the bones of the vault are removed piecemeal; hence successful restoration of the head is rather difficult.

## Book Reviews

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PROTOZOOLOGY. A MANUAL FOR MEDICAL MEN. By JOHN GORDON THOMSON and ANDREW ROBERTSON. Cloth. Price, \$11. Pp. 376. New York: William Wood & Company, 1929.

This latest addition to the rapidly increasing number of protozoological texts claims uniqueness in that it is written for the medical men of the tropics and is not solely a zoological treatise. Following an introduction of ten pages dealing with the fundamental structure and division of the metazoan and protozoan cell, the main portion of the book (268 pages) is devoted to the consideration of the protozoan species of medical importance. Seven sections (fifty-five pages) are then devoted to forms the systematic position of which is doubtful, such as the sarcocysts, various intracellular bodies (*Anaplasma*, *Bartonella*, etc.), the toxoplasmas, the spirochetes and the spirillum of rat-bite fever. The final sections contain a discussion of laboratory technic (twenty-four pages), a glossary of derivations and definitions (six pages) and references (three pages).

The various sections are not encyclopedic, but the main facts are carefully selected. In line with this method of condensation, comparatively few references to original authors are given in the text, and the bibliography is largely a list of texts and special monographs. Similarly, the treatment of various purely zoological questions, such as nomenclature, is reduced to a minimum, but questions such as those of cultivation, diagnosis and pathology are treated in a well rounded manner. The authors are particularly to be commended on their inclusion of such sections as "Fallacies and Puzzles in Blood Examination" and "Common Objects in the Stools Other Than Protozoa," which serve to warn the student against many of the pitfalls of diagnosis. Furthermore, the material in the main sections is admirably selected, and consists, in general, of accurate morphologic accounts of the parasites, their life history, methods of diagnosis and, in the case of the pathogenic protozoa, the pathology of the resulting infections. The detailed account of the pathology is the unique feature of the work and should be especially appreciated by medical students, for whom it is primarily intended. Although the main emphasis is placed on the forms living in man, considerable attention is given to such parasites of animals as the Texas fever organism, *Trypanosoma lewisi* and many others.

The entire treatment reflects the judgment of authors with long teaching experience who are well versed in the advances made by recent investigators. In the reviewer's opinion, the book is well adapted for the particular class of students for which it is intended. It is not intended for, nor will it fill the needs of, more advanced students or specialists as well as some of the other textbooks of protozoology.

The volume is excellently printed, illustrated and indexed. Among the illustrations are four superbly colored plates and a large number of photomicrographs. Many of the latter are admirable, but some hardly enhance the value of the work and might have been either omitted or replaced by simpler drawings.

BRAIN MECHANISMS AND INTELLIGENCE. A QUANTITATIVE STUDY OF INJURIES TO THE BRAIN. By K. S. LASHLEY. Price, \$3. Pp. 184. Chicago: The University of Chicago Press, 1929.

This is the first volume of a series of monographs on the work of the Behavior Research Fund in Chicago, which was inaugurated to conduct research in problems of human behavior. The influence of varying grades of cerebral destruction in the white rat was studied for a variety of functions. The list of chapter headings is illuminative of the scope of the work: theories and problems; general methods; the influence of cerebral lesions on the capacity to learn; the influence of cerebral

injuries on retentiveness; the course of learning in deteriorated conditions; the effects of cerebral lesions subsequent to the formation of the maze habit: localization of the habit; the relation of reduced learning ability to sensory and motor defects; discussion of experimental results; the nature of deterioration following cerebral lesions; comparison of the rat with other forms; the neural mechanisms in adaptive behavior. It concerns in fact a new and noteworthy experimental approach to the study of cerebral physiology. The style is clear and concise. There are thirty-three figures in the text, eleven of which are plates with diagrams of lesions in the different series of experiments, and a select bibliography. The following inferences are drawn by the author from his results:

"The learning process and the retention of habits are not dependent upon any finely localized structural changes within the cerebral cortex. The results are incompatible with theories of learning by changes in synaptic structure, or with any theories which assume that particular neural integrations are dependent upon definite anatomical paths specialized for them. Integration cannot be expressed in terms of connections between specific neurons.

"The contribution of the different parts of a specialized area or of the whole cortex, in the case of nonlocalized functions, is qualitatively the same. There is not a summation of diverse functions, but a nonspecialized dynamic function of the tissue as a whole.

"Analysis of the maze habit indicates that its formation involves processes which are characteristic of intelligent behavior. Hence the results for the rat are generalized for cerebral function in intelligence. Data on dementia in man are suggestive of conditions similar to those found after cerebral injury in the rat.

"The mechanisms of integration are to be sought in the dynamic relations among the parts of the nervous system rather than in details of structural differentiation. Suggestions toward a theory of the nature of these forces are presented."

That intelligence is a single dynamic function of the nervous system rather than a summation of diverse functions separately located in the brain is a startling and revolutionary conclusion that will stimulate greatly the work in experimental psychology.

A HISTORY OF THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY.  
By P. M. ASHBURN, Colonel, Medical Corps, U. S. Army; author of "The Elements of Military Hygiene." With an Introduction by Surgeon-General Merritte W. Ireland. Price, \$5. Pp. 448. Cambridge: Houghton Mifflin Company, The Riverside Press, 1929.

The book was written in response to the wish of Surgeon-General Ireland for a somewhat popular account of the growth and achievements of the Army medical department, now under his charge. While writing, the author was librarian of the library of the Surgeon-General's office, now the Army Medical Library, and as such, in ready command of a vast amount of material, which he has used to good advantage, with wise restraint. The book is divided into six parts, covering periods as follows: The first century, 1775 to 1873; up to the Spanish-American War; that war itself; up to the World War; the World War itself; and finally, the period thereafter to 1928. There can be no question as to the accuracy of the presentation, which runs along smoothly and easily and gives the reader a faithful picture of the development of the department in response to emergencies, as well as to the general demand of medical progress. The great achievements of the department through the work of Beaumont, Billings, Reed and other great men are given due consideration and emphasis. Probably pathologists would have enjoyed a fuller account of the Army Medical Museum, its treasures and mode of working. Be that as it may, Ashburn's book gives the story of the War Department in a form that will attract its officers and all who are interested in the development of the kind of service it represents.

## Books Received

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STERILIZATION FOR HUMAN BETTERMENT. A Summary of Results of 6,000 Operations in California, 1909-1929. By E. S. Gosney, B.S., LL.B., and Paul Popenoe, D.Sc. Price, \$2.00. Pp. 194. New York: The Macmillan Company, 1929.

SELECTED READINGS IN PATHOLOGY FROM HIPPOCRATES TO VIRCHOW. Edited by Esmond R. Long, Professor of Pathology, University of Chicago. Price, \$4.00. Pp. 301, with 25 plate illustrations. Springfield, Ill.: Charles C. Thomas, 1929.

THE ARMY MEDICAL BULLETIN. Pp. 179. Medical Field Service School, Carlisle Barracks, Penn., 1929.

The Army Medical Bulletin is published from time to time for the dissemination of information relating to administration, preventive medicine, medical field service, and other matters of a medico-military nature. The present number contains a synopsis of the work of the army medical research boards in the Philippines, with abstracts of articles published on the results of this work.

BRAIN MECHANISMS AND INTELLIGENCE. A Quantitative Study of Injuries to the Brain. By K. S. Lashley. Price, \$3.00. Pp. 183. Chicago: The University of Chicago Press, 1929.

KLINISCHE EPIKRISEN zugleich beiträge zur Differentialdiagnose. Herausgegeben von Norbert Ortner und Alfred Luger. I. Abdominelle Krankheitszustände. Bearbeitet von L. Berger, J. Blösch, G. Holler, A. Kautzky, V. Kollert, E. Lauda, A. Luger, N. Ortner, K. Paschkis, P. Rezek and E. Silberstern. Price, 8.80 marks. Pp. 151, with 3 illustrations. Vienna: Julius Springer, 1929.

This book consists of ten clinical histories by members of the second medical clinic of the University of Vienna on cases of abdominal disease, supplemented by reports of autopsies. The detailed discussion of clinical manifestations in the light of the revelations post mortem should be illuminating and instructive.

KLINISCHE LABORATORIUMSTECHNIK. Herausgegeben von Prof. Dr. Theodor Brugsch und Prof. Dr. Alfred Schittenheim Zweite, vollständig neu bearbeitete Auflage der "Technik der Speziellen Klinischen Untersuchungsmethoden." IV. Band Unter Mitarbeit von O. Bénesi, K. Birnbaum, H. Elsner, J. Fischer, V. Frühwald, H. C. Jacobäus, F. H. Lewy, W. Meisner, A. Moll, O. Moog, O. Rumpel, H. Runge, J. Schnierer, A. Schwenkenbecher, H. Strauss und W. Wolff. Paper. Price, 50 marks. Pp. 2101 to 2840, with 328 illustrations. Berlin and Vienna: Urban & Schwarzenberg, 1929.

SCIENTIFIC METHOD. Its Function in Research and in Education. By Truman Lee Kelley, Professor of Education and Psychiatry, Stanford University. Cloth. Price, \$2.50. Pp. 195. Columbus: Ohio State University Press, 1929.

FELLOWSHIPS AND SCHOLARSHIPS FOR ADVANCED WORK IN SCIENCE AND TECHNOLOGY. Bulletin of the National Research Council no. 72. Second edition. Compiled by Callie Hull and Clarence J. West. Price, \$1.50. Pp. 154. Washington, D. C.: The National Research Council, 1929.

REPORT OF THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA. By Herbert Fox, M.D., Pathologist. Pp. 65. Philadelphia: 1929.

This report covers the year ending Feb. 28, 1929. It contains interesting notes on animals of special importance, infectious diseases, neoplasms, special subjects of pathologic importance (such as gastric ulcer, leukemia in the monkey and nocardial infection in skunks) and parasites. It is the policy of the institution to place available material at the disposal of scientific workers.

# ARCHIVES OF PATHOLOGY

VOLUME 8

NOVEMBER, 1929

NUMBER 5

## EARLY GASTRIC CANCER \*

WILLIAM L. A. WELLBROCK, M.D.

ROCHESTER, MINN.

Hauser,<sup>1</sup> in 1883, was the first to note histologic evidence of the fact that gastric cancer may arise in chronic gastric ulcer, and since that time there have been numerous and varying contributions to the literature on this subject. Today, with the newer methods and advances in gastric surgery, earlier and smaller lesions may be studied. The examination of fresh unfixed material gives a more accurate cytologic and histologic picture, thereby reducing the number of borderline diagnoses and permitting the earlier recognition of malignant changes. In the past, a diagnosis of cancer of the stomach was not made until all the classic signs and symptoms of a malignant tumor were present. In this stage, treatment is at best only palliative, although certain patients may live for years after resection. In general, the postoperative good results are indirectly proportional to the size of the growth. Therefore, it behooves the medical profession to attempt all means which allow the recognition of the smallest malignant condition.

### MATERIAL

In this study 100 excised and resected small gastric lesions were used. The gross appearance of each lesion was noted. Fresh frozen sections were made from various portions and stained with Unna's polychrome methylene-blue ripened according to Terry's rapid method. Fixed frozen sections stained with hematoxylin and eosin were also studied.

### OBSERVATIONS IN CHRONIC GASTRIC ULCER

The chronic gastric ulcer is a local circumscribed dissolution of the continuity of the gastric wall involving all layers, and is usually round, funnel-shaped or U-shaped. The size varies from a few millimeters to several centimeters in diameter. In the mucosa of the borders of such ulcers, the capillaries are congested and there is an increase in the interstitial tissue, or fixed connective tissue, with lymphocytic infiltration. The tubules are usually tortuous, and some, especially those nearest the

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\* Submitted for publication, Sept. 5, 1929.

\* From the Section on Surgical Pathology, the Mayo Clinic.

1. Hauser, Gustav: The Chronic Gastric Ulcer, Its Cicatrization, and the Relationship Between the Development of Gastric Carcinoma, Leipzig, F. C. W. Vogel, 1883.

muscularis mucosae, are sometimes dilated. This torsion and budding of the tubules give the histologic appearance of glandular hyperplasia. The epithelium that lines the tubules usually shows some regeneration, and occasionally there may be seen one or more heterotropic glands beneath the muscularis mucosae. The muscularis mucosae is often thickened and blends with the muscularis and scar tissue in the crater. The submucosa is also thickened and infiltrated with inflammatory fibrous tissue. The muscularis in the base of the ulcer is almost completely replaced by fibrous tissue; it is hyalinized in older cases, and it is tilted upward toward the border of the ulcer, blending with the muscularis mucosae. This traction of the muscular coats, together with the scar tissue in the crater, often causes overhanging of the mucosa. The subserosa is usually thickened by fibrous tissue infiltration. In the upper portion of the concave base may be observed degenerated mucus, cell debris, degenerated epithelium, bacteria, small round cells, polymorphonuclear leukocytes, plasma cells, fibroblasts and fibrocytes. The vascularity of the crater varies. In some cases it presents numerous small capillaries; in others, fewer larger well formed capillaries, and in still others few capillaries or blood spaces. Throughout, and in any part of the ulcer or in its edges, in mucosa, crater, musculature or subserosa, there may be aggregations of lymphocytes, sometimes forming definite groups with germinal centers. The blood vessels supplying the ulcer are frequently thickened.

The causes of gastric ulcer are not known. Injury caused by or associated with arterial spasm, hemorrhage in local tissue or embolic infarcts may play a large part. Portal stasis with variations in local blood pressure may possibly produce such hemorrhage with necrosis. Chemical and thermal trauma may be causative factors.<sup>2</sup> Rosenow<sup>3</sup> produced acute and subacute ulcers in animals by injection of bacteria obtained from foci of infection in cases of peptic ulcer. Mann<sup>4</sup> produced similar ulcers, however, in other ways. Experimentally produced ulcers have not been observed becoming chronic and remaining so; for the occurrence of chronicity there must be interference with local circulation. This may be the reason why chronic gastric ulcers have never been produced experimentally.

Vascular change probably plays an important part in preventing ulcers from healing. The more intense the acute and subacute inflammatory reaction the more rapid the healing process. If the inflammatory

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2. Aschoff, L.: Ueber die mechanischen Momente in der Pathogenese des runden Magenschwürs und über seine Beziehungen zum Krebs, *Deutsche med. Wchnschr.* **38**:494, 1912.

3. Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, *J. Infect. Dis.* **19**:333, 1916.

4. Mann, F. C.: Production and Healing of Peptic Ulcer, *Minnesota Med.* **8**:638, 1925.

process is diminished or entirely absent, the alkalinizing influence of the exuding serum of the capillary bed in the crater neutralizing the local action of the gastric juice will not be apparent. In such a case connective tissue will not be formed as a result of inflammatory reaction, and the ulcer will affect the deeper structures until the serosa is reached and perforation occurs. There is a constant struggle between the healing and the ulcerative forces.

The mucosa lining the stomach contains relatively simple tubular glands.<sup>5</sup> There are three or four different kinds of cells lining these tubules with quantitative variations in different portions of the stomach. The first type of cell is the surface secreting cell, which includes the cells lining the surface of the ducts leading from the deeper portions of the glands. The second is the mucoid cell, of which there are two closely allied groups, namely, the cardiac and pyloric glands and the mucoid cells that occur in the large intervening fundus, where they are intermingled with the peptic and oxyntic cells; they occupy chiefly the superficial or upper half of the gland tubule, but may occasionally be seen almost throughout the tubule. The oxyntic cells, which chiefly occupy the upper portion of the gland, are found between the mucoid cells; in the deeper portion of the gland, they take up a parietal position. The peptic cells are found within the deeper part of the gland. From the study of new-born cats it is found that the peptic cells arise from cells of the mucoid type and are the last to develop. The mucoid cell is a stage in the genesis of the peptic cell. The peptic cells and the oxyntic cells are the most highly differentiated and specialized.

It would be difficult to prove that a benign gastric ulcer may change into a carcinomatous or malignant ulcer unless one could produce experimentally chronic gastric ulcer, then produce cancer in the ulcer, and then show that all the conditions of the experiments are comparable with the conditions that arise in human beings.<sup>6</sup> Hauser attempted in a rather convincing manner to demonstrate histologically that the change does occur; he distinguished atypical tubular proliferation from true cancer.

Friedlander<sup>7</sup> concluded from his investigations that atypical epithelial hyperplasia may occur where regenerative processes are taking place, either in the epithelium-bearing membrane itself or in the surrounding structures. These processes are either producing granulation tissue or specific tumor. Von Hanseemann<sup>8</sup> believed that the epithelium

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5. Lim, R. K.: The Gastric Mucosa, *Quart. J. Micr. Sc.* **66**:187, 1922.

6. MacCarty, W. C.: Chronic Ulcer and Carcinoma of the Stomach, *Am. J. M. Sc.* **173**:466, 1927.

7. Friedlander, quoted by Hauser (footnote 1).

8. Von Hanseemann, D.: Ueber die Funktion der Geschwulstzellen, *Ztschr. f. Krebsforsch.* **4**:564, 1906.



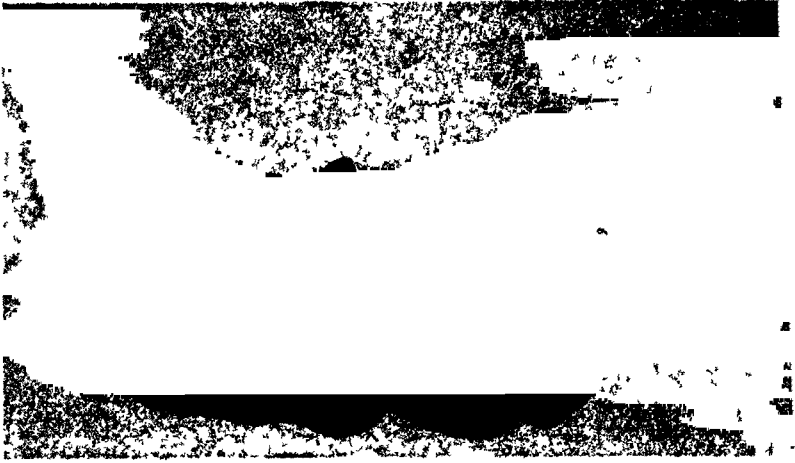


Fig. 1.—Simple chronic gastric ulcer (1.5 by 1.5 by 1 cm.).

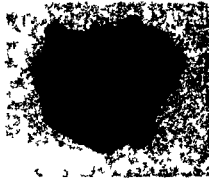


Fig. 2.—Chronic gastric ulcer (1 cm. in diameter), with cancer in mu



Fig. 3.—Chronic gastric ulcer (6 by 4 by 2 cm.) with cancer in mucos

returns to its embryonic state and acquires a significant reproductive property which belongs to undifferentiated tissue. If at this time it is excited to proliferate, it produces new and atypical tissue known as cancer. MacCarty described the earliest cytologic changes in the tubules under the term secondary cytoplasia.<sup>9</sup> By a close study of these changes in the tubules it is possible to differentiate easily between heterotropic glands and early cancer.<sup>10</sup>

#### DIFFERENTIAL POINTS IN HISTOLOGIC DIAGNOSIS

It is probably a mistake to speak of the degeneration of ulcer into cancer. Cancer is biologically a defensive constructive process, although



Fig. 4.—Normal heterotropic gland in submucosa.

for the organism as a whole it forms a purposeless, functionless and eventually fatal new growth. The cancer cell is an undifferentiated or partially differentiated cell and the greater the amount of differentiation the lower the malignancy; the less the differentiation the higher the malignancy.<sup>11</sup>

9. MacCarty, W. C., and Broders, A. C.: Chronic Gastric Ulcer and Its Relation to Gastric Carcinoma, *Arch. Int. Med.* **13**:208 (Feb.) 1914.

10. Maniscalco, Giuseppe: Sulla etiologia e patogenesi del cancro, *Riforma med.* **21**:340, 1905.

11. Broders, A. C.: Squamous-Cell Epithelioma of the Lip: A Study of Five Hundred Thirty-Seven Cases, *J. A. M. A.* **74**:656 (March 6) 1920; Squamous-Cell Epithelioma of the Skin: A Study of 256 Cases, *Ann. Surg.* **73**:141, 1921; The Grading of Carcinoma, *Minnesota Med.* **8**:726, 1925.



Fig. 5.—Heterotopic glands in muscularis mucosae and submucosa with some atypical epithelial cells;  $\times 75$ .



Fig. 6.—Section of ulcer shown in figure 2; early cancer limited to the mucosa is shown.

In carrying out this routine of differential diagnosis of benign and malignant ulcers, the highest powers of the microscope must be used, because malignant and regenerative cells resemble each other closely.<sup>12</sup> Both cells are spheroidal or ovoidal and usually larger than a normal epithelial cell. The nuclear membrane of the regenerative cell is more delicate and the size of the nucleolus in proportion to the volume of the nucleus is smaller, whereas the nuclear membrane of the malignant cell is more dense and the nucleolus, which is often multiple, is hyperchromatic and larger in proportion to the volume of the nucleus.<sup>13</sup> In sinuses of lymph nodes, the distinction must be made from lymphoblasts, endothelioblasts and fibroblasts. In the tubules of the gastric

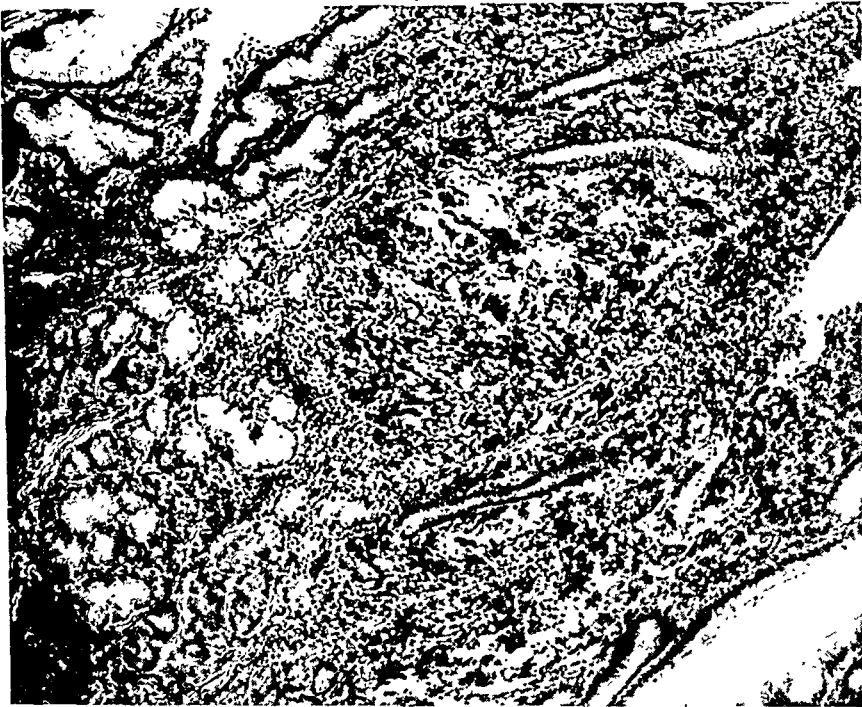


Fig. 7.—Section of ulcer shown in figure 3; early cancer limited to the mucosa is shown.

mucosa, regenerative cells occupy a position which is perpendicular to the plane of the stroma; their long axes radiate from the center of the tubule like the spokes of a wheel. Malignant cells, on the contrary, are irregularly arranged in relation to each other and the plane of the stroma, with the long axes usually parallel to or bent toward the basement membrane. The malignant cell is indistinguishable from the cells of secondary cytoplasia.<sup>13</sup>

12. MacCarty, W. C.: The Histogenesis of Cancer of the Stomach, *Am. J. M. Sc.* **149**:469, 1915.

13. MacCarty, W. C.: The Cancer Cell and Nature's Defensive Mechanism, *Surg. Gynec. Obst.* **41**:783, 1925.



Fig. 8.—Border of ulcer; cancer in mucosa is shown;  $\times 75$ .

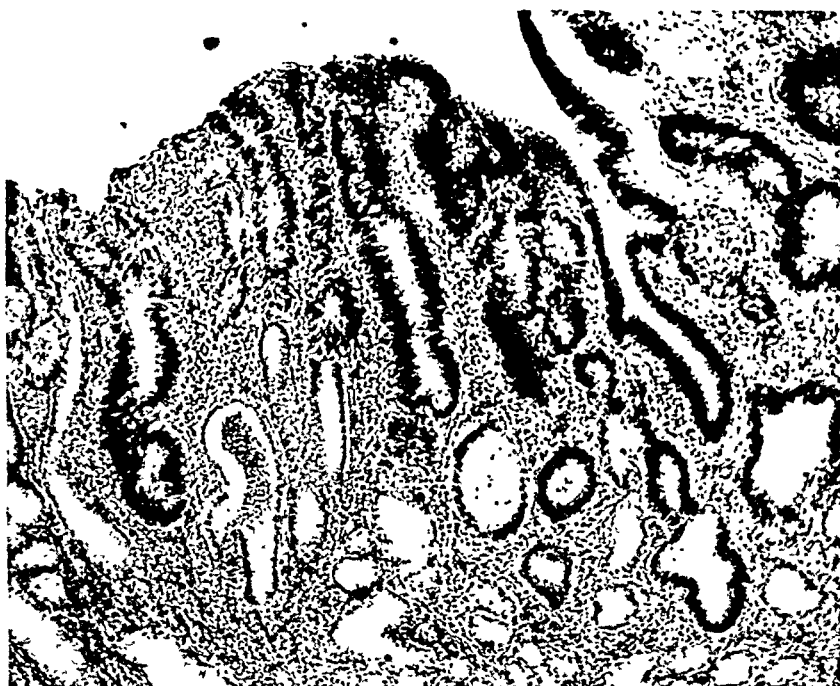


Fig. 9.—Border of ulcer; cancer in mucosa is shown;  $\times 75$ .

The earliest changes must be sought for in the cells lining the tubules of the gland. If the cells of secondary cytoplasia are seen breaking through into the stroma, the condition is termed tertiary cytoplasia.<sup>14</sup> Ulcers in which secondary cytoplasia was found alone have not, in this study, been considered malignant. But if in the borders of small and large ulcers tertiary cytoplasia, in addition to secondary cytoplasia, was found, this condition has been designated early cancer.

In the illustrations of early cancer are seen the cytologic changes described (figs. 1 to 10); this malignant change is entirely limited to the mucous membrane. Secondary cytologic changes are present with some of the growth or proliferation and migration, showing the formation of new glandular tissues. Various so-called types of cancer are

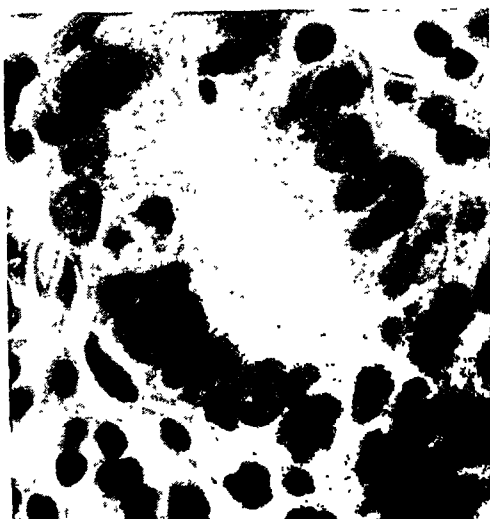


Fig. 10.—Cells having the appearance of malignant cells within the tubule;  $\times 700$ .

seen: the type composed of simple rather small cells diffusely growing, the glandular or adenomatous type and the adenomatous-colloid type.

#### CONCLUSION

Differential clinical diagnosis of benign and malignant gastric ulcers is notoriously defective.<sup>15</sup> All chronic callous gastric ulcers are suspected of being carcinomatous and should be treated as such before, and at the time of, operation. The use of the microscope is the only means of distinguishing simple chronic gastric ulcer from early gastric cancer. The diagnosis cannot be made by clinical means, roentgenoscopy or the appearance of the gross specimen.

14. MacCarty, W. C.: A Biological Conception of Neoplasia, Its Terminology and Clinical Significance, *Am. J. M. Sc.* **157**:657, 1919.

15. Mayo, W. J.: The Calloused Ulcer of the Posterior Wall of the Stomach, *Ann. Surg.* **72**:109, 1920.

## ERYSIPELAS OF THE STOMACH \*

HARRISON S. MARTLAND, M.D.

AND

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Recently, we had the opportunity of observing before death, and finding at autopsy, a case of primary idiopathic phlegmonous gastritis of streptococcal origin in which the gross appearance of the stomach suggested to one of us (M) the possibility of its being erysipelas. The histologic changes were identical with those seen in erysipelas of the skin or that of mucous membranes, and the streptococcus occurring in enormous numbers in the submucosa was positively identified by Birkhaug as belonging to the group of *Streptococcus erysipelatis*.

Phlegmonous gastritis is said to be a rare disease. Known since the time of Galen, it was first accurately described in 1820 by Cruveilhier.<sup>1</sup>

In 1919, Sundberg<sup>2</sup> published a review of 215 case reports which he had collected from the literature. In 1927, Gerster<sup>3</sup> added forty-eight additional case reports, making a total of 263 recorded up to 1927. Most cases, however, are never reported. In any large autopsy service, the various types of phlegmonous gastritis and enteritis, while uncommon, occur with such frequency as to be hardly considered rare.

The cases reported have usually occurred in persons between the ages of 20 and 60 years. The disease is about three times as frequent in men as in women.

Phlegmonous gastritis occurs in diffuse form, extending over the entire stomach wall, or in localized, circumscribed form. Of the 185 reports of cases of phlegmon in Sundberg's collection, 158 were of the diffuse, and twenty-seven of the circumscribed, form. Streptococcus is by far the commonest organism recovered (in 70 per cent of the cases). Staphylococci, pneumococci, *Bacillus coli* and *B. subtilis* have been isolated in a few cases, usually of the localized form. Some of the reported cases were associated with old or recent lesions in the mucosa

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\* Submitted for publication, Sept. 5, 1929.

\* From the pathological department of the City Hospital, and the office of the Chief Medical Examiner of Essex County, N. J.

\* Read before the New York Pathological Society at the New York Academy of Medicine, New York, Nov. 8, 1928.

1. Cruveilhier: *Traité d'anatomie pathologique en générale*, Paris, 1862, vol. 4, p. 485.

2. Sundberg, H.: *Nord. med. ark.* **51**:303, 1919.

3. Gerster, J. C. A.: *Phlegmonous Gastritis*, *Ann. Surg.* **85**:668 (May) 1927.

of the stomach, particularly with ulcer and carcinoma. Others were said to have followed abdominal blows or trauma. Cases of the primary idiopathic form, which is the most common and most important, showed no gross lesion in the mucosa and were considered by MacCallum<sup>4</sup> and others as definitely streptococcal in origin. The submucosa of the stomach was found to be enormously thickened by a tense inflammatory exudate loaded with streptococci.

According to Gerster,<sup>3</sup> the typical symptoms of the so-called idiopathic form are "sudden onset, with profound prostration, high fever, chills, intense epigastric pain and tenderness, repeated severe vomiting and more or less local rigidity." Peritonitis occurs in from 60 to 70 per cent of the cases. Diagnosis is rarely made before operation, the condition usually being mistaken for acute perforated gastric ulcer, acute pancreatitis or acute cholecystitis.

Phlegmonous gastritis in most cases is an acute lesion and usually fatal. Recovery, however, may take place. The average duration of the disease is one or two weeks, but in several cases death has occurred within a few hours of onset. The mortality is 92 per cent (Sundberg). The disease also occurs in subacute and chronic forms. Such cases are often localized, not extensive and usually associated with ulcer or carcinoma. Numerous eosinophils may be present in the exudate. Whether a benign form of leather bottle stomach (linitis plastica) may result from the healing of localized or diffuse forms is questionable, as most cases of this disease are really sclerosing fibrocarcinomas of the stomach. It is possible, however, that some cases of hour-glass stomach represent the end-stages of healed phlegmons.

The absence, in most cases, of any obvious portal of entry to explain the infection has forced most recent observers to fall back on the hematogenous routes. Some authors also give as explanation of the infection the more fashionable, but equally vague and unproved, selective affinity of streptococci for certain tissues. Phlegmonous gastritis has occasionally been observed during epidemics of puerperal sepsis, notably one in Prague in 1847. Cases have also been seen following erysipelas or furunculosis, or as sequelae to smallpox, scarlet fever, polyarthrititis and pyemia. They sometimes occur as a postoperative complication.

To our knowledge, phlegmonous gastritis has never been interpreted as erysipelas of the stomach, with perhaps one exception. Sachs<sup>5</sup> stated that in the pathologic museum of the Mount Sinai Hospital, New York, there is a specimen of phlegmonous gastritis to which it was Libman's

4. MacCallum, W. G.: Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 489.

5. Sachs, Benjamin: In discussion of authors' paper at meeting of New York Pathological Society, Nov. 8, 1928.



practice to refer as erysipelas of the stomach. Libman<sup>6</sup> informed us that this occurred in a patient who five weeks before death had an erysipelas of the leg. He was of the opinion that the lesion looked like erysipelas. At that time (1909), little was known concerning the serologic grouping of the streptococci.

Aside from this case, we are unable in a careful search of the literature to find any evidence that erysipelas of the stomach has ever been described. Erysipelas commonly occurs on the face, head, scrotum and legs; around surgical wounds and around the navel of new-born infants. It is a well known fact, however, that erysipelas is not confined to the skin. Holmes<sup>7</sup> held that most cases of facial erysipelas start in the mucosa of the nasal cavities, possibly from latent infection of the nose, nasal sinuses, etc. Erysipelas may often extend to the mucous membranes of the mouth, nose, eyes, pharynx, middle ears, larynx, rectum and vagina. From the mouth it has sometimes spread to the lungs, pharynx and esophagus. The frequent infection of women during childbirth has long been recognized, as well as the danger of the erysipelatous process spreading to the uterine mucosa and adnexa.

While phlegmonous gastritis is unusual, we do not feel that this warrants the report of a case unless there is some outstanding new feature. A case in which the gross appearance and histologic features are identical with erysipelas and in which, for the first time, there is bacteriologic and serologic identification of the organism present, as of the group of *Streptococcus erysipelatis*, warrants, we believe, such a record.

#### REPORT OF CASE

*History.*—E. H., a white woman, aged 72, was admitted to the Newark City Hospital in a dying condition. Seven days before death, the patient was suddenly seized with cramplike pains localizing in the upper left quadrant of the abdomen. She was nauseated and she vomited twice. Pain became intense. Two days later, the family physician was called in, and the pain was relieved somewhat by opiates. Five days later, the patient was again seen by the family physician, who found the abdomen markedly distended and tympanitic. The bowels had not moved for five days. There was tenderness in the left hypochondrium extending into the epigastrium, and on palpation the sensation of a tumor mass. On account of no improvement in the general condition of the patient, she was sent to the hospital, where she lived only five hours. Examination at the hospital showed an elderly white woman in a moribund condition. There was great distention and tenderness all over the abdomen. Only stimulative treatment was administered. A clinical diagnosis of generalized peritonitis, possibly due to a malignant abdominal growth, was made.

*Autopsy.*—In order to obtain permission for an autopsy, the undertaker was allowed to embalm the body by the arterial method. This, however, did not seri-

6. Libman, Emanuel: Personal communication to the authors.

7. Holmes, Charles: Ann. Otol. Rhin. & Laryng. 16:457, 1907.

ously interfere with the correct interpretation of the lesions, as the autopsy was performed immediately afterward. Autopsy showed the body of a somewhat emaciated woman, aged 72, with a greatly distended abdomen. There were no marks of injury on the skin, no rash and no edema. Aside from cloudy swelling in the heart muscle, liver and kidneys, a terminal pulmonary edema and vascular changes due to age, the important observations were those of the stomach and peritoneum.

The stomach was greatly distended. Near the pylorus, it felt as if there was a large stenotic growth. The whole stomach wall was leathery and did not collapse. There were no enlarged glands among the lesser or the greater curvature, and no enlargement of the periportal nodes. The esophagus was free. On opening the stomach, which was empty, one saw a remarkable condition. There were marked thickening and edema of the stomach wall, most marked in the pyloric

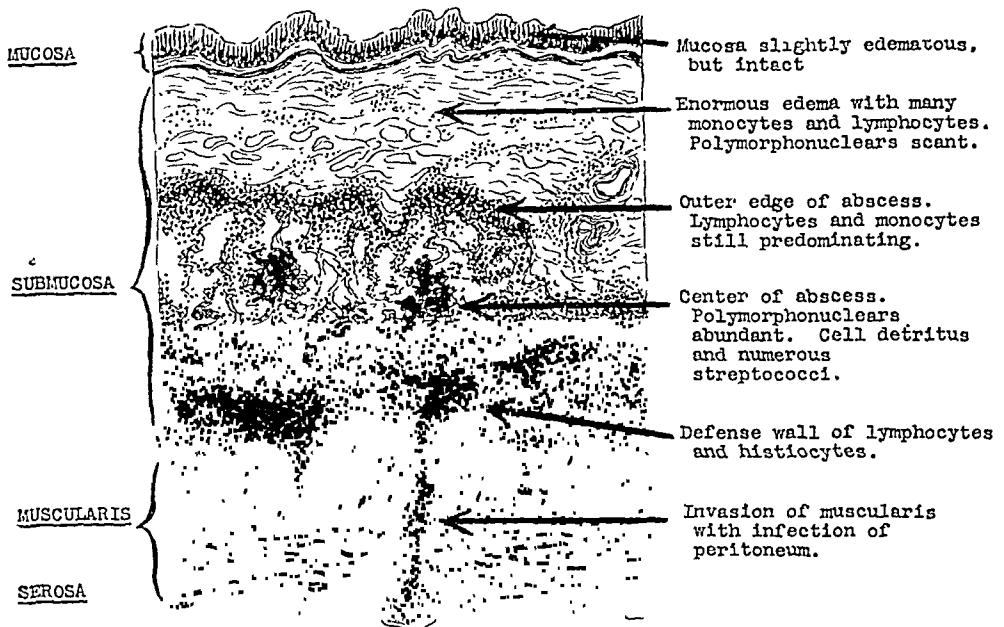


Fig. 1.—Schematic diagram of stomach wall showing the location and character of the lesion.

half, where the wall was  $\frac{1}{2}$  inch (1.27 cm.) thick. The mucosa, in spite of the fact that it was bleached by the embalming, was still a diffuse scarlet hue, and showed only an occasional mucosal and submucosal hemorrhage. The rugae were obliterated and ironed out by the edema. There were no recent or old ulcers and no macroscopic abrasions. Close inspection of the stomach wall showed that over one half of the thickening was due to distention of the submucosa by a watery, purulent exudate. The mucosa was but slightly swollen. In the submucosa, lying between the mucosa and the internal circular muscular coat, which was plainly visible, there was a large amount of grayish, watery, purulent fluid which could be pressed out. The submucosa had a somewhat honey-combed appearance due to a partitioning off of this purulent fluid by connective tissue trabeculae. In places, multiple small abscesses were seen in which the fluid was thicker and more creamy. Grossly, the muscularis, aside from the edema, was free from changes. Over the serosa was a plastic purulent exudate. This

suppuration extended diffusely thoroughout the entire submucosa of the stomach, but was more pronounced in the pyloric half. It was sharply demarcated above by the esophageal orifice and below by the pyloric valve. The mucous membrane of the esophagus and duodenum appeared normal. There was considerable purulent fluid in the pelvis and abdominal gutters and there was extensive fibro-purulent exudate over the stomach and loops of small intestine, gently gluing them together in places.

Death was caused by phlegmonous gastritis, with terminal generalized suppurative peritonitis through extension from the stomach by continuity.

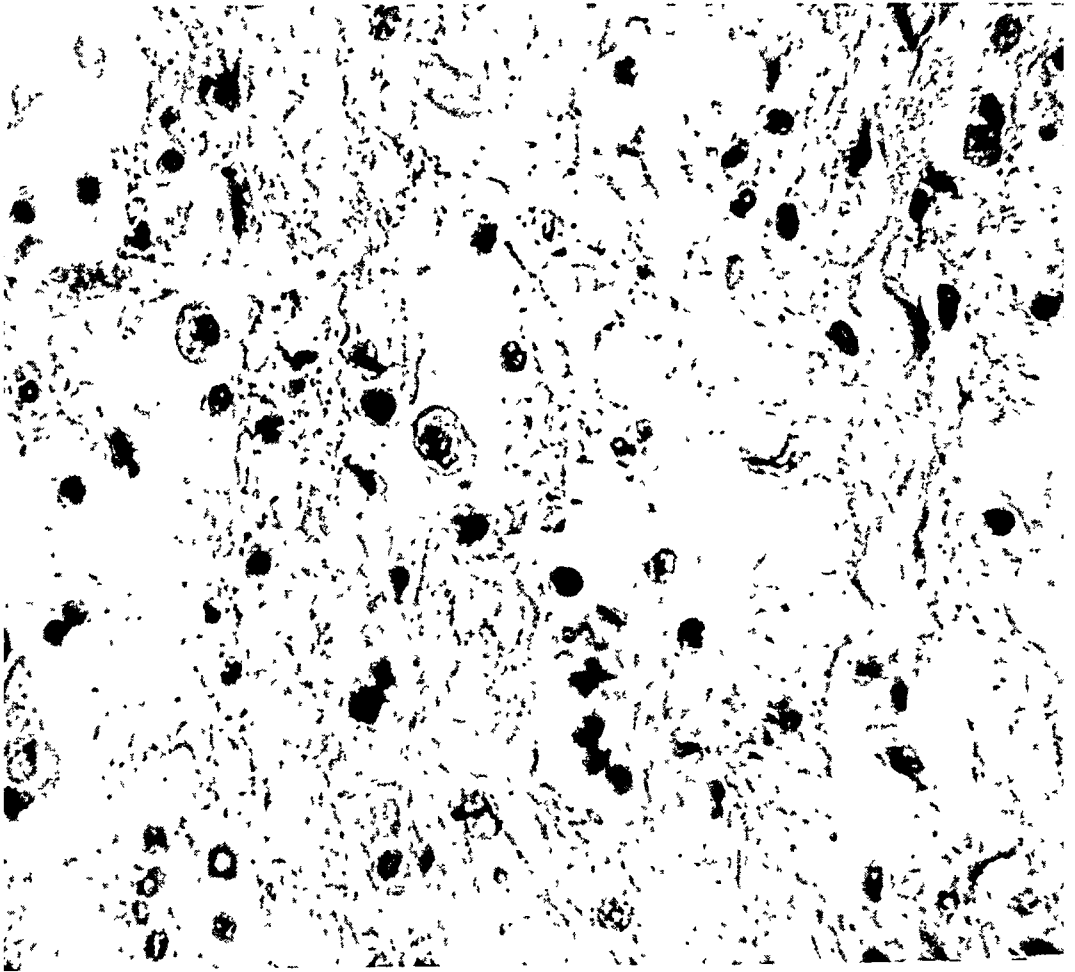


Fig. 2.—Photomicrograph showing inner portion of the submucosa. The distention of the tissue spaces with edema and the presence of an exudate composed chiefly of lymphocytes and monocytes may be noted. Streptococci were not numerous in these areas;  $\times 480$ .

*Bacteriology.*—Smears made from the fluid pressed from the submucosa of the stomach showed a great number of gram-positive streptococci. No other organisms were present.

As the body had just been embalmed, the isolation of this streptococcus was expected to be difficult. However, by transferring portions of the stomach wall over in large quantities of broth we finally obtained, in pure culture, a hemolytic, long-chained streptococcus.

*Histology.*—Microscopic sections were made through the entire thickness of the stomach wall. The mucosa was shown intact and was only slightly edematous; it was practically free from any cellular exudate. The muscularis mucosa was intact, but in places it was edematous and swollen, and showed a slight infiltration with lymphocytes and histiocytes. The submucosa was greatly thickened, forming over one half of the entire thickness of the stomach wall. Its inner portion was comparatively free from cellular exudate, but there was enormous edema, the fluid distending the tissue spaces and widely separating them. The little cellular

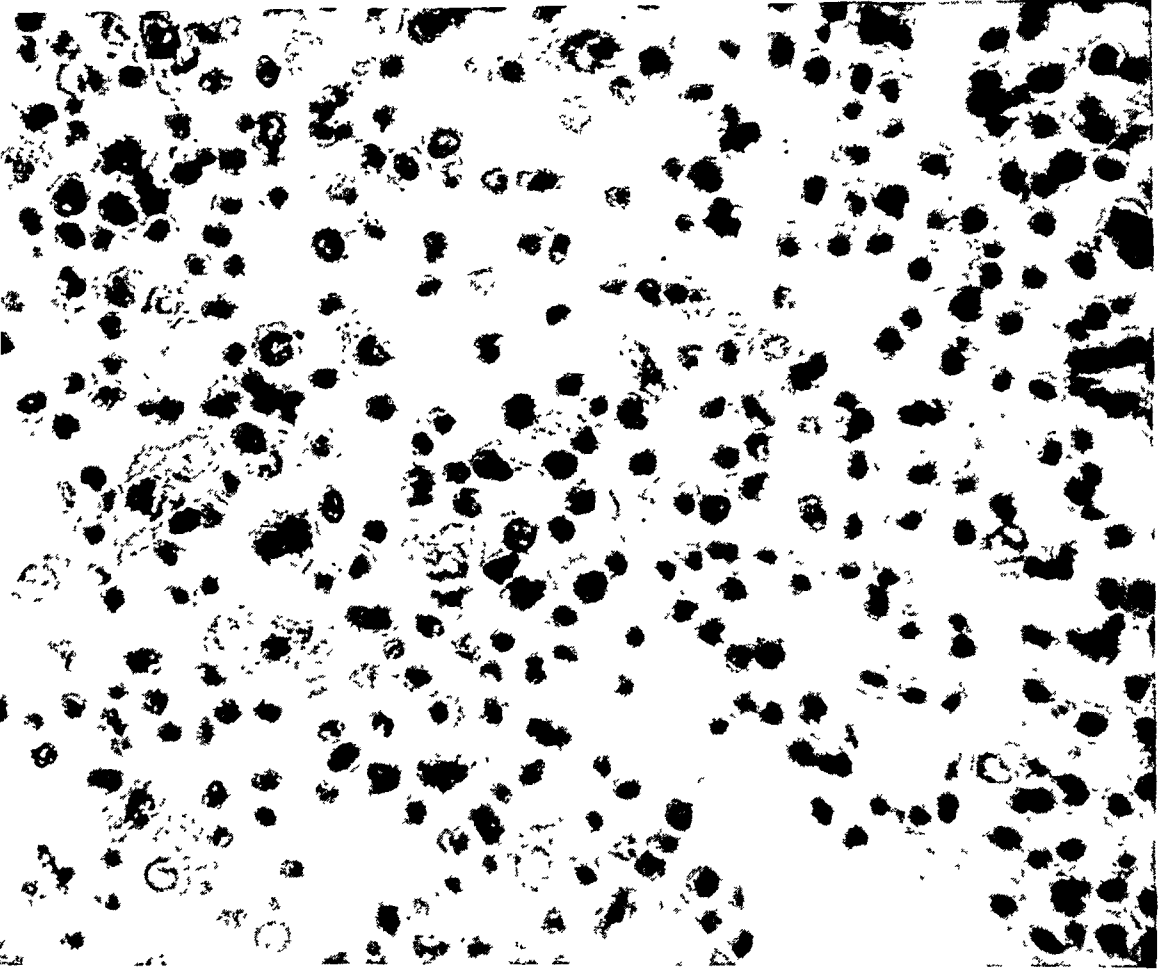


Fig. 3.—Photomicrograph showing deeper portions of submucosa. The extensive suppuration may be noted. While numerous polymorphonuclears are present, the lymphocytes and monocytes predominate. Numerous streptococci are present in these areas;  $\times 480$ .

exudate present was composed chiefly of lymphocytes and monocytes. No definite relationship to the lymphatics could be made out. Few polymorphonuclears were present. As one approached the middle of the submucosa, the exudate became abundant, and more polymorphonuclears were present. This became so marked as to form small abscesses. The periphery of these areas was formed chiefly of lymphocytes and monocytes, and the central portions contained chiefly polymorphonuclears. In the center of many of these areas there was extensive necrosis

with numerous polymorphonuclears and considerable cellular detritus. Gram stains showed numerous streptococci in these areas, and they were scant or absent in other portions of the stomach wall. Near the internal circular layer of the muscularis there was a strong defense wall composed of many histiocytes and lymphocytes and few polymorphonuclears. In places, this cellular exudate filtered through the muscle bundles of the muscularis and extended to the serosa, where there was edema with beginning suppurative peritonitis. The muscularis itself was free. Practically no eosinophils were present.

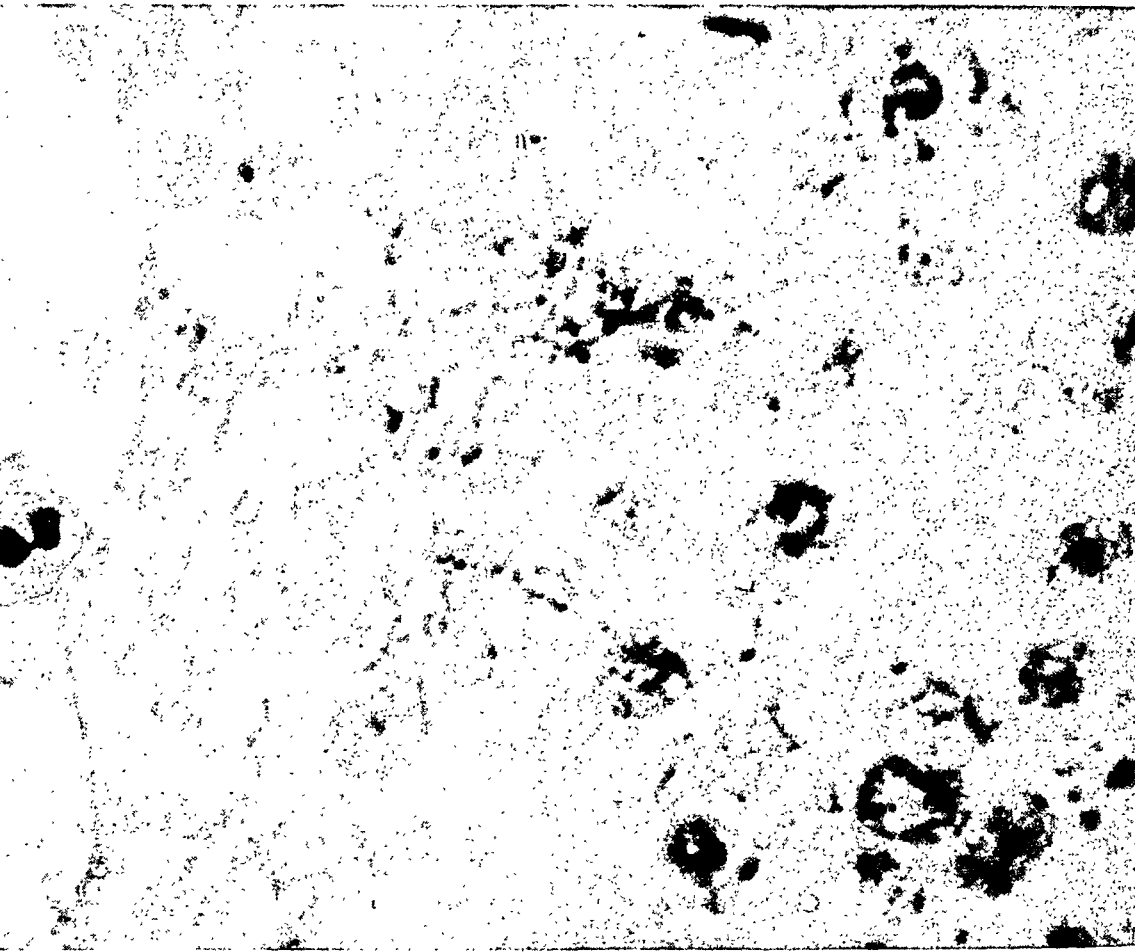


Fig. 4.—Photomicrograph taken from a central area of suppuration in the submucosa. Necrosis, cell detritus and numerous streptococci may be noted. Gram-Weigert stain;  $\times 1,050$ .

#### IDENTIFICATION OF STREPTOCOCCUS BY BIRKHAUG

An agar slant containing a pure culture of a gram-positive hemolytic streptococcus recovered from the submucosa of the stomach at autopsy by Dr. Lloyd Riggs, assistant bacteriologist to the Newark Department of Health, was sent to Dr. Konrad E. Birkhaug, associate professor of bacteriology, University of Rochester, for identification.

Birkhaug was not able to agglutinate this culture properly with his standard erysipelas immune serums because of its quick spontaneous precipitation in broth during the first ten hours of growth. He resorted then to the absorption of known antibodies for *Streptococcus erysipelatis* and found that the strain removed the agglutinins for three of four of his standard strains of *S. erysipelatis*. He repeated this process twice and obtained identical results. Birkhaug also attempted to remove the agglutinins in the antiserum for *Streptococcus scarlatinae* with this strain and found that the original titer of 1:2,560 was reduced only to 1:1,280 with the homologous strain of *S. scarlatinae* (Dochez, N. Y. 5). The final criterion of typical *S. erysipelatis* is its constant production of toxin in Douglas' tryptic digest broth. The five days' culture of this strain was filtered through a Berkefeld V candle. In a series of titrations in the skins of persons susceptible to the toxin of *S. erysipelatis*, he found that a potent exotoxin was produced, 1 cc. of which contained more than 10,000 skin test doses. In proper dilutions with the antitoxin for *S. erysipelatis*, this toxin was completely neutralized. Putting these facts together, Birkhaug stated, "It appears that your strain is definitely related to the serological types of *Streptococcus erysipelatis*."

This is the first time, therefore, that the streptococcus isolated from a case of phlegmonous gastritis has been positively identified as belonging to the erysipelatis group. This is due entirely to the painstaking, classic identification by Birkhaug.

#### CONCLUSIONS

A case of primary idiopathic phlegmonous gastritis has been described, in which the appearance of the stomach was identical with that of the stomach in most cases described in the literature. There were no gross lesions of the mucous membrane, such as ulcer, carcinoma, abrasions or other injuries. The inflammation was diffuse, extending over the whole stomach, but limited almost entirely to the submucosa. The diffuse blushing of the mucosa, the ironing out of the rugae by edema and the thick, edematous condition of the submucosa filled with a watery, grayish fluid containing innumerable streptococci with occasional small abscess formations suggest the gross appearance of erysipelas, and the picture is similar in every way to that of extensive erysipelas of the skin with cellulitis of the subcutaneous tissues.

The sharp demarcation of the suppurative process in this case by both the cardiac orifice and the pylorus, both of which have a mucosa which is rather tightly bound down, is similar, for instance, to the sharp demarcation and stoppage of facial erysipelas at the lower border of the mandible.

Histologic examination showed the lesion to be almost entirely confined to the submucosa. It is characterized by extensive boggy edema, in which the cellular exudate is composed chiefly of lymphocytes and monocytes. The polymorphonuclears are abundant only in the central areas, where formation of abscesses occurs, and where there is necrosis, with cell detritus and innumerable streptococci. This histologic picture is identical with that seen in erysipelas.

The identification of the streptococcus by Birkhaug, as belonging serologically to the group of *Streptococcus erysipelatis*, completes the case and proves, as nearly as can be, that some forms of phlegmonous gastritis may be considered erysipelas.

# CUTANEOUS LESIONS (INFECTIOUS GRANULOMAS) ON THE FEET OF ALBINO RATS\*

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AND

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The occurrence of well defined ulcers on the bony prominences of the lower forelegs of dogs maintained on diets deficient in vitamin B complex has been reported by Cowgill, Stucky and Rose (1929<sup>1</sup>); these lesions healed promptly when this food factor was replaced. The parallelism between the occurrence of the lesions and the dietary deficiency was definitely suggestive. The authors noted that the ulcers did not appear in all the animals subjected to the experiment. Furthermore, they noted scars of presumably identical lesions in other dogs that were not subjects of experiments in nutrition. They recognized that the factors of pressure and local injury were necessarily uncontrolled variables. The purpose of this communication is to report the occurrence of lesions on points of pressure on the feet of white rats maintained on adequate diets.

The photographs accurately portray the lesions. They usually occurred in the situation shown in the illustrations. Only in a few instances were they observed on the forefeet and on the anterior portion of the hind feet. As a rule, they were bilaterally symmetrical.

In the early stages, they appeared as slightly elevated, pale red, sub-epidermal nodules. The overlying epidermis was intact. The following changes then occurred successively: loss of the overlying epithelium, formation of a superficial ulcer with a base of granulation tissue, and finally a marked overproduction of granulation tissue. The surfaces of the lesions were deep red and relatively free from exudate, and bled after slight trauma. In a few instances, the productive nature of the lesions was less evident, the bases of the ulcers being flat or somewhat depressed (fig. 1).

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\* Submitted for publication, Sept. 5, 1929.

\* From the Laboratory of Physiological Chemistry and the Department of Surgery, Yale University.

\* Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Cowgill, G. R.; Stucky, C. J., and Rose, W. B.: Physiology of Vitamins: Cutaneous Manifestations Related to Deficiency of Vitamin B Complex, Arch. Path. 7:197 (Feb.) 1929.



The lesions were generally oval or spherical and sometimes were pedunculated or sessile. The shape was probably determined by such external factors as the location, the pressure and the amount of irritation.

Microscopic sections confirmed the gross observations. The earliest change was a slight thickening of the dermis, which was followed by a loss of the overlying epidermis, the formation of an ulcer with a base of granulation tissue and finally the overgrowth of granulation tissue to



Fig 1—An ulcerative lesion (left) and a proliferative lesion in profile (right);  $\times 2\frac{1}{2}$

form a protuberant lesion. In some instances, a typical depressed ulcer with a flat base developed. There was a thin layer of a fibrinopurulent exudate on the external surfaces and an infiltration of the granulation tissue by polymorphonuclear leukocytes.

The character of the granulation tissue varied with the age and the size of the lesions. In the more advanced stages, the superficial portions showed a delicate meshwork of capillaries, but the deeper areas showed a large amount of fibrous tissue. The essential nature of the proliferative lesions was that of an infectious granuloma (figs 2 and 3).

The larger granulomas showed some evidence of epithelial proliferation, although there was nothing suggestive of epithelial invasion of the surrounding tissue.

The lesions in our animals were similar to the granuloma pyogenicum of man (Michelson, 1925<sup>2</sup>), the most characteristic feature of which is the proliferation of the granulation tissue to form a small pedunculated or sessile nodule. They differ from the lesions described by Cowgill, Stucky and Rose in that the latter were definitely depressed



Fig. 2—Large granuloma in the advanced stage,  $\times 2\frac{1}{2}$ .

ulcers without evidence of granuloma formation. In some instances, similar ulcers were observed in our animals. The differences in the nature of the ulcerative and granulomatous changes may be due to such variable factors as species of animal, duration of experiment and infection.'

The observations here recorded were made on a large series of rats used in an experiment in nutrition. Three adequate rations were

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<sup>2</sup> Michelson, H. E.. Granuloma Pyogenicum Clinical and Histologic Review of 29 Cases, Arch. Derm & Syph. 12:492 (Oct.) 1925.

employed varying only in the concentration of protein (casein) as follows: 18, 60 and 85 per cent. Most of the animals had been subjected to unilateral nephrectomy; a few were controls on which laparotomy only had been performed. There were three age groups at the time of operation—90, 180 and 360 days—and the experimental period extended for 56 days and 150 days longer. The rats were kept in cages with wire screen bottoms during their entire life.

At the outset, it can be said that the lesions occurred irrespective of the diet consumed. The rats that were 90 days old when the experiment began were practically free from lesions; those 180 days old showed early changes rather uniformly, and the animals 360 days of age exhibited severe ulcers in almost every case. These were more advanced in the 150-day, than in the 56-day, period. It appears, therefore, that the incidence of the lesions is correlated with the factors accompanying age rather than with diet. As the older rats are heavier, it would seem that



Fig. 3—Longitudinal section through the granuloma shown in figure 2. The lighter portions near the base are areas of epithelial proliferation;  $\times 2\frac{1}{2}$ .

pressure on the feet and the length of time are important factors in the pathogenesis of these ulcers. It is possible, too, that the tissues of older animals are rendered more susceptible to injury during senescence.

In view of the dietetic adequacy of the rations employed and the absence of any evidences of nutritive disturbance in the animals here discussed, it is suggested that caution be exercised in deciding whether or not the ulcers observed on bony prominences of animals maintained for relatively long periods under experimental conditions necessarily have a specific dietary significance. On the other hand, it is reasonable to expect that a nutritive disturbance might lower the resistance of body tissues to such an injury as that described and that improvement in the local lesions would be observed along with disappearance of the general manifestations of the deficiency.

The lesions described in the present communication are probably not due to the lack of a specific nutritional factor, but to repeated slight traumas and a superimposed infection with pyogenic organisms.

# MULTIPLE SPLEEN COMBINED WITH OTHER CONGENITAL ANOMALIES

REPORT OF TWO CASES \*

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Accessory spleens are not infrequently encountered at necropsy. I have seen them in about 10 per cent of bodies during routine post-mortem examination. They are small and usually single, and the spleen itself is normally developed. The appearance of multiple spleen without a fully developed spleen is apparently rare.

Albrecht<sup>1</sup> reported 400 spleens in a man, aged 25, with the real spleen situated higher than usual and adherent to the diaphragm. These accessory nodules were scattered all over the peritoneum. Kaufmann<sup>1</sup> mentioned the case of Faltin and Kuttner, in which a splenectomy was done for a gunshot wound that had done crushing injury to the spleen, and five years later about 1,000 spleens were found on the peritoneum. Beneke<sup>2</sup> thought such cases were the result of trauma with splenic regeneration from implantation. Pool<sup>3</sup> mentioned the occurrence of multiple spleens with malformation of other viscera. He cited Hyrtl's four cases, with transposition of the viscera. In these cases, spleens were broken up into from five to eleven smaller nodules. Garrod, according to Pool, reported two cases of heart disease with multiple spleens, 4 and 9, respectively. He likewise mentioned Helly's specimen, which is preserved in the anatomic museum at Vienna; in this there was a bilobular spleen with eleven accessory spleens. Other unusual anatomic variations of great interest have been reported.

The splenic anomalies that I present are rare. I can discover no other example of the condition in the first case, in which there was a combination of multiple spleens with congenital stenosis of the bile ducts and cirrhosis of the liver. The second case parallels somewhat those of Garrod, since it showed a congenital cardiac lesion with bilobular spleen and ten accessory portions.

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\* Submitted for publication, June 14, 1929.

\* From the Department of Pathology, St. Luke's and Children's Mercy Hospitals.

1. Albrecht, cited by Kaufmann, Edward: *Pathology for Students and Practitioners*. Authorized translation by Stanley P. Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1.

2. Beneke, cited by Kaufmann (footnote 1).

3. Pool, E. H.: *Surgery of the Spleen*, New York, D. Appleton & Company, 1923.

## REPORT OF CASES

CASE 1.—C., an infant, was jaundiced at birth. The delivery was easy and spontaneous. The cord came off on the sixth day after birth. On the ninth day, the child began to bleed from the umbilicus. On the twelfth day, she was brought to the hospital with a slow oozing from the navel. The skin and sclera were markedly jaundiced and she was emaciated. The mother admitted having had syphilis, which she had contracted from her first husband. She had been treated and pronounced cured. There was one living child, aged 5. The family history was of no significance otherwise.

The infant received 50 cc. of the father's blood intramuscularly, and four days later was given 150 cc. intraperitoneally. She progressed poorly until about the eighteenth day of life when, following venipuncture of the left external jugular, she began to have rapid respiration and became paler, and the heart beat became rapid. The impression was that the child was bleeding from some hidden site. She also bled considerably from the needle puncture in the neck and there was oozing into the surrounding cervical tissues. The results of the laboratory examinations were negative, except for the fact that the child was shown to have 17,550 white cells per cubic millimeter of blood. No differential white cell counts or red cell counts were made. The Wassermann reaction was negative.

At the necropsy, which was performed shortly after death, the most outstanding external feature was a striking jaundice of the skin, sclera and mucous membranes. There were large areas of hemorrhage in the region of the jugular vein on the neck, where blood had been withdrawn for examination, with slow oozing into the surrounding tissue. There was also a hemorrhage around the umbilicus, and hemorrhages in the tissues of both hips where injections had been made. Apparently there had been little tendency to clot. The hemorrhage was found to extend into the subcutaneous tissues of the neck, from the chin to the clavicle, throughout the left anterior angle of the neck. The blood from the heart had the viscosity of water, and was not clotted. Small hemorrhages were found scattered over the pleura, and in the parenchyma of the lung many were seen. The lungs were not fully expanded. The thymus was atrophied. The main changes otherwise were found in the abdomen. Masses of fetal adhesions were found over the gallbladder, connecting it with the transverse colon and duodenum. The liver was large, measuring 10.5 by 8 by 6 cm., and weighing 156 Gm. It was hard and showed a slightly wrinkled capsule and was deeply jaundiced. On cross-section, it cut with great resistance, and showed a high grade cirrhosis of periportal type. The gallbladder was little more than a fibrous cord with a small lumen. Both the common and the hepatic duct were completely occluded.

Histologically, the liver showed marked fibrosis, with a tendency to a periportal arrangement. Considerable inspissation of bile was noted in the canaliculi and smaller ducts.

The spleen was divided into fourteen separate and distinct nodules by fetal adhesions, these nodules varying in size from 20 to 2 mm. in diameter. Each nodule received a branch of the splenic artery.

Histologically, these spleens showed nothing unusual or particularly abnormal. There were some foci of myeloid cells in the pulp.

CASE 2.<sup>4</sup>—W., an infant, was born normally. The mother had had two former pregnancies. The first pregnancy resulted in a stillborn infant. At the second, she bore twins, but they died before birth, the mother having developed a severe

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4. Permission to report case 2 was obtained from Dr. Waller Hook.

toxemia and labor having been brought on prematurely by bag induction. The child in question had attacks of cyanosis and shallow breathing, and died about forty-eight hours after birth.

At necropsy, the heart was large, weighing 37 Gm. The right auricle and ventricle were markedly distended and hypertrophied. The left ventricle was small, and no aorta was found leaving it. The foramen ovali was wide, and no valve was present. The pulmonary artery gave branches to the lungs and then



Fig. 1.—Fourteen separate splenic nodules, each with a distinct blood supply from a branch of the splenic artery. Twice natural size.

continued on down, becoming the systemic aorta. The lungs were but partially expanded. All the abdominal viscera showed deep hyperemia, the liver being particularly large. The gallbladder was covered with dense fetal adhesions, which communicated with the transverse colon and the duodenum, as in the first case.

The spleen showed the most interesting picture. It was broken up into ten separate nodules, separated by fetal adhesions, the spleen proper being bilobular and showing three notches. It measured 40 by 22 by 7 mm. The smaller nodules varied from 15 to 2 mm. in diameter.

## COMMENT

The etiology of these anomalies is unknown. Since the spleen is not, embryologically, a lobulated organ, such malformations are difficult to explain. Mention was made by Kaufmann<sup>1</sup> of experiments on monkeys in which multiple spleens were produced through traumatization of the original spleen, the regeneration taking the form of multiple nodules. Faltin and Kuttner's case of multiple spleens following a crushing injury to the spleen, and the subsequent growth of 400 implants, is



Fig. 2.—Ten separate splenic nodules, each supplied with a branch of the splenic artery. Twice natural size.

suggestive. The presence of fetal adhesions around the gallbladder and the spleen in both my cases suggests a possible intra-abdominal fetal injury.

## SUMMARY

Two cases of multiple spleen are reported, one case showing fourteen separate nodules, the other ten. One case occurred in conjunction with congenital stenosis of the extrahepatic bile ducts and the other in connection with a congenital cardiac malformation.

Both cases showed fetal adhesions dividing the lobules and many dense adhesive bands in the gallbladder region. This suggests a possible intra-abdominal fetal injury as an etiologic factor in the production of these anomalies.



# RENAL INSUFFICIENCY IN AMYLOID DISEASE\*

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AND

S. G. MAJOR, M.D.

ST. PAUL

Renal insufficiency in amyloid disease has been observed for many years, and contracted kidneys in amyloid disease were first described by Wagner in 1861.<sup>1</sup> Since that time many cases of contracted kidney have been recorded in which the outstanding feature was a massive deposit of amyloid in the glomeruli, in the vessel walls and inside the basement membranes of the collecting tubules. Many of these cases, however, were recorded before the study of blood chemistry was a recognized clinical procedure, while others give no indication that blood chemistry was studied or other tests of renal function performed, the evidence of renal insufficiency being based entirely on anatomic and strictly clinical evidence of kidney damage. The earliest of these reports were from Klebs,<sup>2</sup> and other cases were reported by Schalong,<sup>3</sup> Fahr,<sup>4</sup> Wegelin<sup>5</sup> and Danisch.<sup>6</sup>

There seem to be three generally accepted conceptions of this pathologic entity. The first was advanced by Fahr,<sup>7</sup> who believed that the amyloid kidney is a form of nephrosis. He divided the morphologic changes in the amyloid kidney into four stages, with case reports illustrating each stage. In the cases classified as representing the first stage, he found only a minimal amount of amyloid in the glomeruli, together with a moderate degree of albuminous degeneration of the tubules. As representing stage two, he described cases that showed a larger amount of amyloid in the glomeruli, and more marked degenerative changes in the tubules. These degenerative changes included hyaline granules in the renal epithelium and a rather marked deposit of lipid, comparable to that seen in lipid nephrosis. In the

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\* Submitted for publication, June 1, 1929.

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1. Wagner, E.: *Arch. d. Heilk.* **2**:481, 1861.

2. Klebs, E.: *Handbuch der pathologischen Anatomie*, Jena, Gustav Fischer. 1889, vol. 2, p. 623.

3. Schalong, H.: *Virchows Arch. f. path. Anat.* **257**:15, 1925.

4. Fahr, Theodore: *Virchows Arch. f. path. Anat.* **248**:323, 1924; *Berl. klin. Wchnschr.* **55**:993, 1918.

5. Wegelin, C.: *Schweiz. med. Wchnschr.* **56**:716, 1926.

6. Danisch, H.: *Verhandl. d. deutsch. path. Gesellsch.* **20**:307, 1925.

7. Fahr, Theodore: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925.

group that he classified as representing stage three, the kidneys contained large amounts of amyloid in the glomeruli with a consequent narrowing of the capillaries. He stated that in these cases, in spite of the narrowing of the capillaries, many of the glomeruli were still permeable to blood. In the fourth stage, the glomeruli were destroyed, and there was a marked tubular atrophy, which was secondary to the glomerular damage.

Fahr believed that the disease is a toxic process affecting both tubules and glomeruli simultaneously, the primary damage being done to the glomeruli. He also described arteriosclerosis of the vessels as occurring particularly in those cases in which the patients were over 50 years of age, but he thought that this change does not play an important part in the production of contracted kidneys in amyloid disease. Fahr's ideas were closely followed by Danisch<sup>6</sup> in his report of two cases of contracted kidney in amyloid disease. Linder,<sup>8</sup> who reported the best studied case we have been able to find in the literature, agreed with Fahr as to the nephrotic character of the disease. Ophüls<sup>9</sup> and McElroy<sup>10</sup> subscribed to the same theory.

The second conception is that amyloid degeneration occurs in the course of chronic nephritis as expressed by Osler<sup>11</sup> and McCrae,<sup>12</sup> it is "simply an event in the process of a chronic nephritis, most commonly in the chronic parenchymatous nephritis, following fevers or cachectic states." McCrae stated that "amyloid kidney is usually spoken of as a variety of nephritis, but in reality it is a degeneration which may accompany any form of nephritis." MacCallum<sup>13</sup> also believed that amyloid is deposited in "any or all of the changes described in progressive nephritis."

MacCallum also stated, however, that amyloid may appear in an otherwise normal kidney in the course of a general amyloidosis. This idea represents the third conception of the disease, namely, that it is simply a part of a systemic condition in which the damage to the

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8. Linder, G. C.; Maxwell, J., and Green, F. H. K.: Clinical, Pathological and Biological Study of Amyloid Nephrosis, *Arch. Dis. Childhood* 2:220 (Aug.) 1927.

9. Ophüls, W.: Nephritis: A New Series of Cases with a Review of Recent Literature, *J. A. M. A.* 65:1719 (Nov. 13) 1915.

10. McElroy, J. B., in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1927, vol. 6, p. 599.

11. Osler, William, and McCrae, T.: The Principles and Practice of Medicine, ed. 2, New York, D. Appleton & Company, 1918, p. 711.

12. Osler, William, and McCrae, T.: The Principles and Practice of Medicine, ed. 10, New York, D. Appleton & Company, 1926, p. 717.

13. MacCallum, W. G.: Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 302.

kidney may be the most prominent feature. Kaufmann<sup>14</sup> concurred in this opinion, but thought that the process is related to parenchymatous nephritis. The opinions of Frothingham<sup>15</sup> and Richardson<sup>16</sup> also fell in with this conception.

Amyloid has been produced experimentally by many workers. The most constant results are probably obtained by the use of staphylococci, but many other agents both chemical and bacterial have been used. Kuczynski<sup>17</sup> successfully produced the substance in animals by the continuous feeding of nutrose and cheese, and these experiments were repeated successfully by Smetana.<sup>18</sup> Frank<sup>19</sup> produced amyloidosis in animals by the use of the Friedländer bacillus. Many other organisms or their toxins have been used in the experimental production of amyloid, but from a clinical standpoint it is fairly well established that amyloid is most frequently associated with chronic tuberculous lesions, chronic suppuration of bone, syphilis, malignant tumors and leukemia. Wegelin<sup>5</sup> also mentioned its association with Hodgkin's disease.

The exact chemistry of amyloid is not yet thoroughly understood, but the generally accepted view is that advanced by Wells,<sup>20</sup> who believed that amyloid is a combination of chondroitin-sulphuric acid and a protein molecule. He pointed out that there is a high chondroitin-sulphuric acid content in bone and in the lungs, and that in destructive lesions of these tissues there is undoubtedly an excess of this substance in the serum, which is carried to various organs, chiefly the liver, spleen, kidney and heart, where it is combined with the protein molecule. He thought that this substance is carried to the various organs in the serum rather than by the leukocytes, and this idea is supported by the fact that amyloid is never found within the epithelial or connective tissue cells. An entirely different theory was advanced by Smetana,<sup>21</sup> who thought that the deposition of this material has to do with a toxic damage to the reticulo-endothelial system, and he attempted to prove this theory by the injection of india ink into animals in which amyloid had already been produced. In these animals, he found that the

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14. Kaufmann, E.: *Spezielle pathologische Anatomie*, ed. 2, Berlin, Georg Reimer, 1911, vol. 2, p. 844.

15. Frothingham, C.: *Nelson's Loose Leaf Living Medicine*, ed. 2, New York, Thomas Nelson & Sons, 1927, vol. 4, p. 701.

16. Richardson, H. B., in Cecil, R. L., and Kennedy, Foster: *A Text-Book of Medicine*, Philadelphia, W. B. Saunders Company, 1927, p. 904.

17. Kuczynski, M. H.: *Virchows Arch. f. path. Anat.* **239**:185, 1922.

18. Smetana, H.: *Bull. Johns Hopkins Hosp.* **37**:383, 1925.

19. Frank, A.: *Beitr. z. path. Anat. u. z. allg. Path.* **67**:181, 1920.

20. Wells, H. G.: *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1914, p. 378.

21. Smetana, H.: *Proc. Soc. Exper. Biol. & Med.* **24**:187, 1926.

reticular cells did not phagocytose the india ink, whereas in normal animals these cells phagocytosed the ink particles readily. He interpreted this as being indicative of damage to, or abnormal function of, the reticulo-endothelial system.

There can be no question that amyloid is deposited in small quantities in many forms of nephritis, but to confuse these minimal deposits with the massive lesions of the kidney seen in general amyloidosis does not seem justifiable. Kumpf,<sup>22</sup> in a study of fifty cases of general amyloidosis, found practically no evidence of changes in the kidneys other than those produced by a simple deposit of amyloid, and it would seem that the cases of amyloidosis showing evidence of renal insufficiency should be considered, not as cases of nephritis, but rather as cases of a systemic disease in which the kidney has been damaged to such an extent that it may be the primary cause of death, or at least that it may produce the outstanding clinical symptoms.

We are reporting here three cases of general amyloidosis in which renal insufficiency was proved by clinical, chemical and pathologic methods. These cases are reported because this possible termination of amyloid disease seems to be little recognized in this country by either pathologists or clinicians. These cases represent the only proved instances of renal insufficiency in amyloid disease in a series of 11,000 necropsies recorded in the department of pathology at the University of Minnesota.

#### REPORT OF CASES

CASE 1.—A man, aged 27, was admitted to the Ancker Hospital on Sept. 29, 1928, complaining of pain and swelling of the left thigh. He stated that for several days before admission he had been riding on freight trains and that the jolting had aggravated an old draining sinus in the region of the hip. He was admitted to the surgical service, and physical examination showed numerous scars over the long bones and an old draining sinus of the left thigh. The thigh was swollen, red and tender, and at one point there was fluctuation. He had a high fever and a leukocytosis of 40,000. The thigh was incised and a soft tissue abscess was found, arising from a chronic osteomyelitis of the femur. After a few days, the fever subsided and the acute condition of the thigh improved. The patient was transferred to the medical service because the urine was found to contain large amounts of albumin, hyaline casts, leukocytes and erythrocytes. After this observation, the patient was questioned more closely and he stated that for eleven years he had had attacks of acute osteomyelitis involving various long bones, and that he had been told some years before by a physician that he had "Bright's disease." It was then noted that he had a moderate pitting edema of the ankles, which persisted throughout his entire stay at the hospital, but did not increase. The highest measurement of the systolic blood pressure was 105 mm. of mercury, and late in the patient's illness this dropped to 93. An examination of the eyegrounds, November 18, showed normal fundi. A roentgen examination of

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22. Kumpf, A.: Unpublished thesis, Department of Pathology, University of Minnesota, 1929.

the chest showed no evidence of cardiac hypertrophy. Between October 1 and the time of the patient's death, December 16, eighteen urinalyses were done. Albumin was present in amounts varying from one to four plus. The specific gravity ranged between 1.010 and 1.028; hyaline and granular casts, leukocytes and a few erythrocytes were persistently present. Two concentration tests were done to determine the functional ability of the kidneys by combining the Mosenthal and the Volhard water tests. On one occasion, November 5, the range of the specific gravity was found to be between 1.008 and 1.010, and a similar test on November 13 showed a range of from 1.011 to 1.014. Three phenolsulphonphthalein tests, November 2, 9 and 11, showed no elimination of the dye. On four occasions between October 29 and December 6, the blood was examined for urea and creatinine. The readings ranged between 60 and 68.6 mg. of urea nitrogen and between 3.1 and 4.1 mg. of creatinine per hundred cubic centimeters of blood. The patient also showed a rapidly progressive secondary anemia. On admission, the erythrocyte count was 4,210,000 and the hemoglobin content 72 per cent. On December 3, the erythrocyte count was 2,800,000 and the hemoglobin content 56 per cent. In spite of the severe degree of the renal damage, the patient was fairly comfortable until a few days before his death. On December 16, he became stuporous and finally lapsed into coma and died.

From these observations a clinical diagnosis of chronic glomerulonephritis was made, although the low blood pressure and lack of cardiac hypertrophy could not be fitted into the picture.

The necropsy was performed on Dec. 16, 1928. External examination of the body showed a fairly marked degree of emaciation. There was a definite pitting edema of the ankles, and just below the inguinal ligament of the left thigh there was an old surgical incision, measuring 8 cm. in length. This wound was only partially healed, but showed no purulent drainage. There were scars over both greater trochanters, the outer aspect of the left tibia and the lateral surface of the left humerus, as well as over the eighth rib on the right side. These were apparently the result of multiple suppurative lesions of bones. The peritoneal cavity contained 2,000 cc. of a clear serous fluid, and the right pleural cavity contained 1,000 cc. of a similar fluid. The heart weighed 240 Gm., and showed an acute rheumatic endocarditis of the mitral leaflets, and adhesions between the aortic leaflets. The lungs were edematous and showed areas of bronchopneumonia along the posterior borders. The liver weighed 1,820 Gm., but showed no gross evidence of amyloid. The spleen weighed 260 Gm. The organ was firm and the capsule was tense, and, after cutting, the surface was found to be glassy and the corpuscles were not visible. The kidneys weighed 285 and 290 Gm. The capsules stripped easily, and the surfaces of the kidneys were pale and mottled by dark red areas. After the kidneys were cut, the cortices were found to be wide and the markings indistinct. The cortex and the medulla were well defined, the cortex being pale and the medulla dark red. The other organs showed little of interest. The spleen, liver and kidneys contained large amounts of amyloid, as demonstrated by the methyl violet stain. The microscopic picture in the kidneys will be discussed with the observations in the other cases.

CASE 2.—A woman, aged 35, had been married sixteen years and had never been pregnant. She gave a history of many previous infections. In childhood, she had had measles, scarlet fever, variola, pneumonia and "rheumatism." In 1912, she had had a salpingectomy and oophorectomy, and in 1913, an appendectomy. In 1917, osteomyelitis of the left tibia had developed and a curettement of the bone had been done. She was first admitted to the Ancker Hospital in December, 1921. At that time, she stated that she had syphilis and had received

a small amount of treatment in the form of mercury and arsenic. She also described an attack of constricting pain in the abdomen and chest seven years before, which the clinician interpreted as a gastric crisis. The Wassermann reaction of the blood was positive. Her chief complaint at the time of this admission was pain in the chest. A diagnosis of pleurisy and syphilis was made. Urinalysis showed a specific gravity of 1.032, a heavy trace of albumin and a few hyaline casts. She left the hospital against advice, but was again admitted in January, 1923, complaining of generalized abdominal pain. The urine at this time showed a specific gravity of 1.026, four plus albumin, hyaline casts, red blood cells and leukocytes. At this time, she was suspected of having gallbladder disease, but because of the urinary conditions surgical intervention was not deemed advisable. In 1925, however, at a private hospital, she was operated on and an empyema of the gallbladder was drained. Her third admission to the Ancker Hospital was on Nov. 21, 1927. Her complaints then were frontal headache and dyspnea. The headaches had been present for the year prior to her admission and were frequently associated with nausea and vomiting. She also complained of frequency of urination and blurring of vision. Her face was puffy, but there was no edema of the ankles. There was clinical and roentgen evidence of a slight cardiac hypertrophy. The blood pressure on two occasions was 175 systolic and 100 diastolic and 176 systolic and 104 diastolic. The urine showed albumin, casts, leukocytes and red cells. An examination of the blood on November 26 showed 47.6 mg. of urea nitrogen and 2.5 mg. of creatinine per hundred cubic centimeters. The patient also had a severe secondary anemia, the red cell count being 2,480,000 and the hemoglobin content 39 per cent. She again left the hospital against advice, but was readmitted on Dec. 3, 1927. At this time, she was markedly dyspneic, her face was puffy and there was a moderate edema of the ankles. Ophthalmoscopic examination showed albuminuric retinitis. The liver was palpable. Three readings of the blood pressure were 165 systolic and 95 diastolic; 180 systolic and 100 diastolic and 160 systolic and 90 diastolic. The average daily urinary output while the patient was in the hospital was 1,067 cc. Eleven urinalyses showed a specific gravity ranging from 1.014 to 1.024, with albumin varying from one to four plus. Casts, leukocytes and red cells were almost constantly present. Two examinations of the blood showed 116.9 mg. of urea nitrogen and 3 mg. of creatinine per hundred cubic centimeters and 147 mg. of urea nitrogen and 3 mg. of creatinine. The secondary anemia was even more pronounced, the hemoglobin content being 32 per cent and the erythrocytes 2,110,000. The patient gradually lapsed into coma and died on Jan. 10, 1928.

The necropsy was done on Jan. 10, 1928. External examination of the body showed it to be poorly nourished. There was a slight edema of the ankles. There was a midline scar in the lower part of the abdomen, and a second scar in the right upper quadrant of the abdomen. There was a scar over the anterior surface of the left tibia, and the bone was thickened beneath the scar. The peritoneal cavity was filled with a yellow, purulent fluid, containing flecks of fibrin. The pus was uniformly distributed throughout the abdomen, and the coils of the intestine were sealed together. There was no evidence of a primary infectious process in the appendix. The fallopian tubes and ovaries were absent. The uterus was small and appeared normal. The gallbladder was embedded in adhesions, but showed no evidence of an acute infectious process. There was no evidence of gastric or intestinal ulceration, or of diverticulitis, to account for the peritonitis. The pericardial sac contained no free fluid, but the visceral and parietal surfaces were sealed together by a thick layer of fibrin. The heart weighed 355 Gm. The valves and coronary arteries appeared normal. The

myocardium was firm but unusually pale. There was no gross evidence of amyloid. About 100 cc. of serous fluid was present in the right pleural cavity. There was an extensive terminal bronchopneumonia. The liver weighed 1,750 Gm. The methyl violet stain showed it to contain a small amount of amyloid. The spleen, similarly stained, showed no amyloid. The kidneys weighed 125 and 135 Gm. The capsules were thick and edematous. They stripped easily, leaving a finely granular surface. After cutting, the surfaces of the kidneys showed slightly narrowed cortices. The cortical markings were not distinct. The cortex and the medulla, however, were clearly demarcated. There was nothing in the gross appearance of the kidneys to suggest amyloid. The other organs showed nothing of note.

CASE 3.—A man, aged 55, who was acutely ill at the time of his admission to the hospital on Dec. 14, 1928, stated that he had not been well for about eight months. He first noticed swelling of his ankles, which did not incapacitate him. This edema persisted for about three months; then it gradually disappeared. About that time he began to have attacks of vomiting, not associated with pain. These occurred at irregular intervals. At times, he had repeated attacks of vomiting, followed by intervals during which he was symptom-free. His complaint at the time of admission was pain in the left side of the chest. He stated that he had taken cold about a week before, and that he had first noticed the pain about five days prior to his admission. This pain was not constant and was aggravated by deep breathing and by motion. There was no history of tuberculosis, chronic suppuration or syphilis, which might have been interpreted as an etiologic factor in the production of amyloid. He said, however, that he had had rheumatic fever twelve or fourteen years before.

Physical examination showed the patient to be well nourished. He had a Kussmaul type of respiration, and there was moderate cyanosis of the face and fingertips. The ankles were moderately edematous. The heart was enlarged to the right and to the left, and there was a pericardial friction rub. There was dullness at the base of the left lung and a friction rub in the same area. The liver was palpable. The blood pressure was 104 systolic and 50 diastolic on one examination. Ophthalmoscopic examination showed a slight edema of the optic disks. There were no hemorrhages, areas of exudate or vascular changes such as are frequently associated with hypertension. On one occasion, the urine showed four plus albumin, hyaline, granular and waxy casts, and pus cells. Examination of the blood on the day of admission showed 134 mg. of urea nitrogen and 3.9 mg. of creatinine per hundred cubic centimeters. On the day of admission, the carbon dioxide tension was 16 per cent by volume, and on the following day it was 7 per cent by volume. This patient also had a severe anemia, the erythrocyte count being 2,360,000 and the hemoglobin content 50 per cent. Shortly after admission to the hospital, he became drowsy and then stuporous, and finally lapsed into deep coma, and died two days after admission. The clinical diagnosis was sub-acute glomerulonephritis, pericarditis and uremia.

The necrosy was done on Dec. 16, 1928. The body was found to be well nourished and there was no evidence of edema. The peritoneal cavity contained no excess of fluid. The left pleural cavity contained about 500 cc. of a sero-purulent fluid, which was encapsulated in an area comprising the superior and anterior two thirds of the pleural cavity. The balance of the pleural cavity was obliterated by dense fibrous adhesions. The right pleural cavity contained an equal quantity of fluid of similar character. The fluid was encapsulated in the postero-inferior portion of the chest cavity. The visceral and parietal layers of the pericardium were adherent to each other by fibrinous adhesions, giving the

heart a shaggy appearance. The pericardial sac contained about 75 cc. of a purulent fluid. The heart weighed 480 Gm. but this weight included the fibrinous exudate. The weight of the heart itself was estimated as 380 Gm. The mitral leaflets were thickened and nodular, but there was no evidence of acute rheumatic vegetations. The lungs showed a moderate degree of atelectasis and an excess of fluid and blood, but no evidence of consolidation. The spleen weighed 200 Gm. The follicles were prominent, but the organ showed no gross evidence of amyloid. The liver was enlarged, and showed no gross evidence of amyloid. Methyl violet stains of liver showed no amyloid, but those of spleen revealed deposits of this substance about the central arteries. Each kidney weighed 140 Gm. The organs were firm. The capsules were removed without difficulty, leaving a finely granular surface. After cutting, the surface of the kidney showed a definitely narrowed cortex. The cortex and the medulla were well defined. The pelves and the ureters

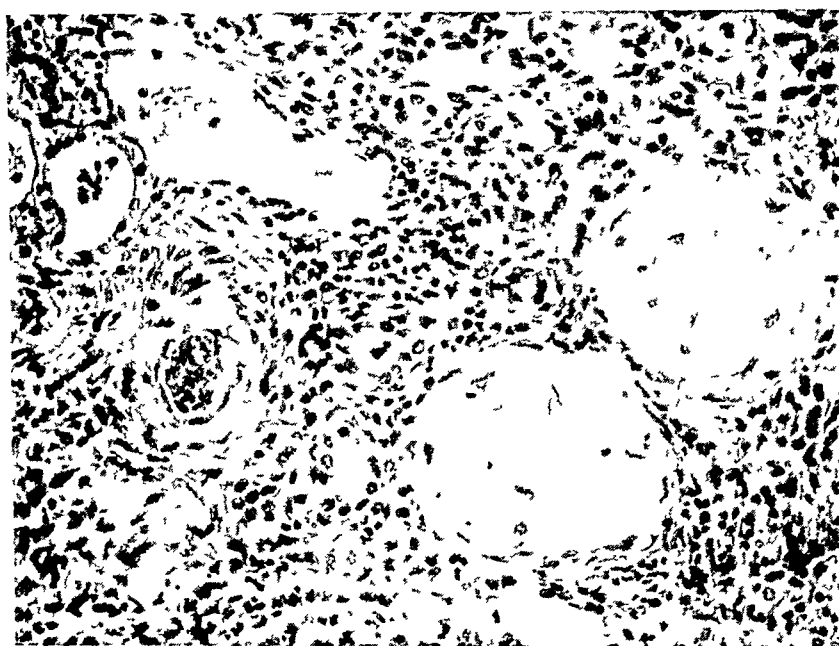


Fig. 1.—A section of amyloid kidney, showing thick-walled vessels and obliterated glomeruli. Hematoxylin and eosin stain.

were normal. Grossly, the kidneys could not be distinguished from kidneys showing a moderate degree of arteriolar involvement in a case of essential hypertension.

*Microscopic Changes in the Kidneys in Cases 1, 2 and 3.*—The kidneys in the three cases described were studied with hematoxylin and eosin, fat and amyloid stains. The microscopic material was fixed in a diluted solution of formaldehyde U. S. P. (1:10), and at the time of study some of the material had been in the fixing fluid fifteen or sixteen months. It was found that the microscopic pictures were materially improved if the sections were treated with ammonium hydroxide prior to staining, after the method of Davidoff. This improvement affected not only the hematoxylin and eosin stains, but also the amyloid stain. Instead of fixing in Zenker's solution, however, as suggested by Davidoff, the tissues for the amyloid stain were fixed in 70 per cent alcohol. This treatment of the tissue, it was found, restored the staining character of the amyloid so that the picture was as good as though the tissues had been fresh. The sections prepared in this way



and fixed in Zenker's solution showed poorer differentiation but more intense staining than those fixed in 70 per cent alcohol. In the preparations fixed in alcohol, the differentiation was distinct.

The microscopic pictures shown in the kidneys in these cases were so similar that one description will suffice for the three cases.

The outstanding deposits of amyloid were found in the glomeruli, and even in these cases representing the advanced stage of the disease there was a marked variation in the amount of amyloid in the individual glomerulus. However, even in those least involved, the capillaries were almost entirely occluded. As shown in figure 1, the glomeruli were a homogeneous mass of amyloid with complete occlusion of the capillary bed. According to Hueter,<sup>23</sup> the amyloid is laid down in the glomerulus between the basement membrane and the endothelium, gradually separating the endothelium from the basement membrane and eventually causing an atrophy of both. He also said that at times amyloid masses are found free in

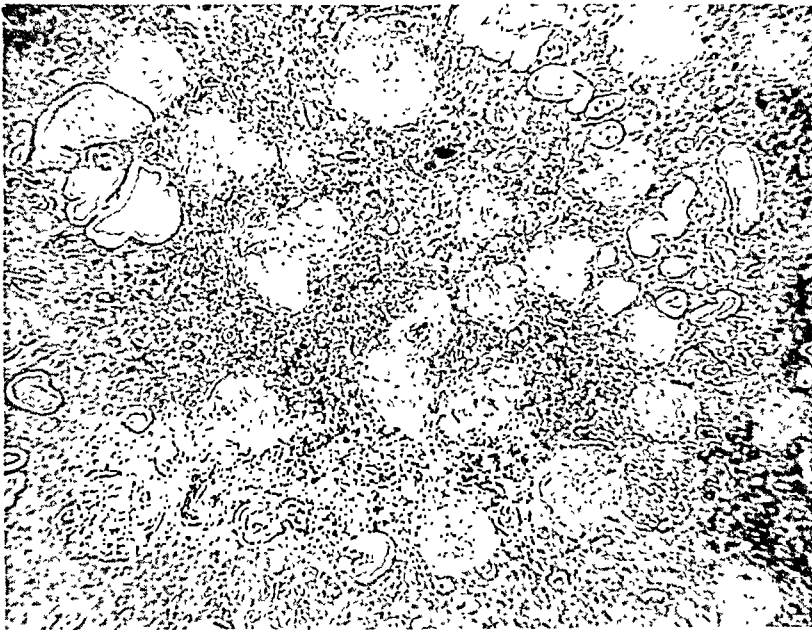


Fig. 2 (case 3).—A section of amyloid kidney, showing tubular atrophy and obliterated glomeruli. Hematoxylin and eosin stain.

the lumen of certain capillary loops. When the deposit of amyloid is so massive, however, the exact mechanism of deposition is not clear. The result, however, is an obliteration of the anatomic structure of the glomerulus with, necessarily, a complete cessation of function. Amyloid was also seen in the walls of many vessels. The larger arteries were not affected, but the smaller vessels, from interlobular arteries down to the afferent arterioles of the glomerulus, frequently showed thickened walls and narrowed lumen due to the deposit of amyloid (fig. 2).

Secondary to this vascular change in the glomeruli and outside of them was a marked atrophy of the tubules. The degree of atrophy varied with the individual case. It was most marked in case 3 (fig. 2) and somewhat less pronounced in case 1. Where the atrophy was not far advanced, the glomeruli themselves were

23. Hueter, C.: *Centralbl. f. allg. Path. u. path. Anat.* **19**:961, 1908.

not so completely closed and the tubules were separated by loose connective tissue. Scattered throughout the atrophic areas were numerous dilated tubules lined with flat epithelium. Many of these tubules contained casts, and a few of the casts took the characteristic amyloid stain with methyl violet. There was a surprisingly large number of inflammatory cells in these kidneys. These cells were both polymorphonuclear and lymphocytic. They were scattered through the atrophic areas in the interstitial tissue, as well as in clumps in the dilated tubules. The inflammatory infiltration is shown in figure 1.

The fat stains showed lipoid material in moderate quantities in the renal epithelium, and a few droplets in the interstitial tissue. The quantity of fat was not as marked as one would expect from Fahr's description, but in these cases there was relatively little epithelium remaining to undergo fatty degeneration, and perhaps in the earlier stages it was to be found in larger amounts.

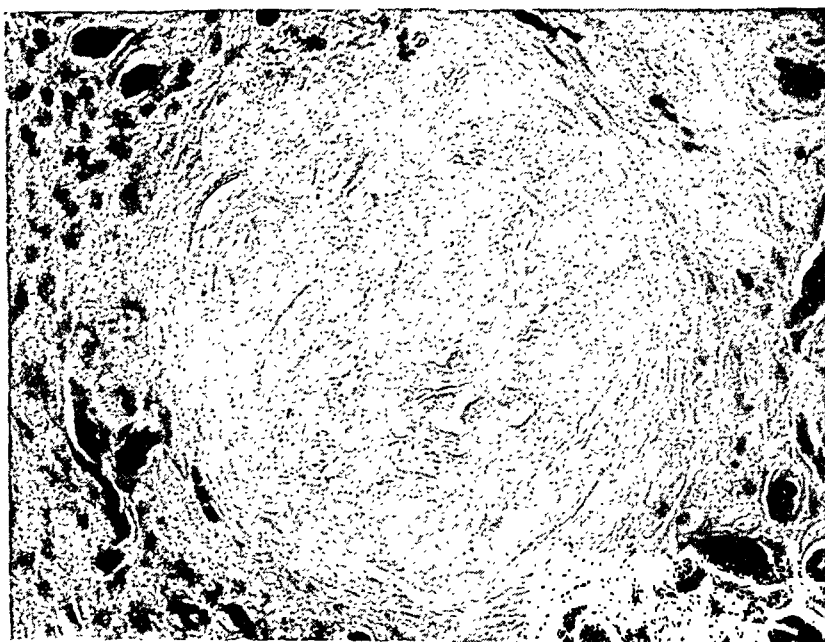


Fig. 3.—Section of amyloid kidney, showing a glomerulus with a transformation of amyloid to hyaline material. The dark stained masses in the center have taken the methyl violet stain. Amyloid stain was used.

In the glomeruli in which the amyloid was oldest, as indicated by the degree of obliteration of the glomerulus and the accompanying tubular atrophy, it underwent a change in its staining characteristics. It failed to take the methyl violet stain uniformly. There were blotchy areas (fig. 3) where the dark stained patches represented the amyloid that had taken the methyl violet stain, while the lighter stained material resembled hyaline. This fading seemed to occur from the periphery of the glomerulus inward, and in most of the glomeruli affected in this way a ring of unstained amyloid was seen in the periphery of the glomerulus. Fahr<sup>7</sup> mentioned the fact that in the far advanced stage, the amyloid is transformed into hyaline, and this is probably the change to which he refers. Wells also stated that, in the opinion of some workers, amyloid is first laid down as a hyaline substance, a precursor of amyloid, but he is of the opinion that this change in the staining character of the amyloid is degenerative, and in the cases studied

here it would appear that the change had occurred after the amyloid had been laid down in the usually recognized form. A similar change was seen in some of the amyloid deposited in the vessel walls.

There was no evidence in the sections to indicate that the kidneys had been involved by any disease process previous to the deposition of the amyloid. Two or three glomeruli showed a slight proliferation of Bowman's capsule, but in no instance was there any evidence of either a proliferative or an exudative inflammation of the glomeruli themselves, and the arterial changes were simply a deposit of amyloid within the vessel walls with no evidence of sclerosis of the usual type.

There were additional cases among our records which showed the same picture as that in the cases described, but the clinical data were too incomplete to prove renal insufficiency. In one of these cases there was an extensive arrested pulmonary tuberculosis. The kidneys were large and showed anatomic damage comparable to the changes in case 1 in the present series. The second case was well studied clinically. Apparently, the etiologic factor in this case was a multiple suppurative arthritis and sinusitis. Apparently, the patient died in uremia, but the last study of the blood, which was made a month prior to death, showed no retention of metabolites.

#### COMMENT

The pathologic process by which the kidneys in amyloid disease reach the state of renal insufficiency shown in these cases is primarily one of vascular damage affecting the glomeruli most severely, but also involving the arteries of small caliber. The condition of the glomeruli in the end-stage of an amyloid kidney is comparable to that seen in advanced glomerulonephritis, in that the capillary bed is occluded. In the case of glomerulonephritis, the capillary bed of the glomerulus is closed either by accumulation of leukocytes or by proliferative changes in the endothelium; whereas, in the amyloid kidney, the capillaries are occluded by a deposit of amyloid under the basement membrane. The effect on the tubules is the same in either case. When the blood supply in the glomerulus is shut off, there is a corresponding atrophy of the associated tubule. The afferent arteries to many of the glomeruli show thickened walls and narrowed lumina owing to the amyloid deposit. In no case was a complete occlusion of an afferent artery observed, and, while in many instances there must have been some reduction in the amount of blood reaching the glomerulus, the damage was primarily glomerular.

It is interesting to note that in case 1, as well as in one of the cases mentioned but not reported in detail, the kidneys were unusually large and showed no evidence of contraction. In all the references to this condition that we were able to find in the literature, the kidneys are described as being shrunken, but apparently the kidney can be damaged sufficiently by the deposit of amyloid to cause renal insufficiency before any contraction occurs. This state of affairs may be comparable to the closure of glomerular capillaries in a subacute glomerulonephritis

in which there is a retention of metabolites, with death from uremia while the kidneys are normal or even slightly larger than normal in size. The deposition of amyloid is usually thought of as a rather slow process, but, in some cases, at least, it is apparently sufficiently rapid to cause capillary closure and death before contraction can occur.

According to Kaufmann,<sup>14</sup> Volhard and Fahr<sup>24</sup> and others, hypertension is unusual in this type of disease, and only one of the three cases here described shows an elevation of blood pressure. The

*Analysis of Three Cases of Amyloid Disease Involving the Kidneys*

Examinations	Case 1	Case 2	Case 3
Age.....	27 years	35 years	55 years
Sex.....	Male	Female	Male
Etiology.....	Chronic osteomyelitis	Syphilis; chronic osteomyelitis	?
Chief complaint.....	Abscess of thigh	Impaired vision	Pleuritic pain
Duration of renal symptoms	?	6 years	8 months
Edema.....	Edema of ankles	Edema of face and ankles	Edema of ankles
Blood pressure.....	93 to 105 systolic	165 systolic and 95 diastolic to 190 systolic and 110 diastolic	104 systolic and 50 diastolic
Eye grounds.....	No examination	Albuminuric retinitis	Slight edema
Kidney function; Phenolsulphonphthalein	No excretion in three tests	No examination	No examination
Concentration.....	1,008 to 1,010; 1,011 to 1,014	No examination	No examination
Blood chemistry:			
Urea.....	60 to 68.6 mg.	47.6 to 147 mg.	134 mg.
Creatinine.....	3.1 to 4.1 mg.	2.5 to 3 mg.	3.9 mg.
Van Slyke.....	No examination	No examination	16 per cent to 7 per cent by volume
Urine:			
Specific gravity.....	1.010 to 1.028	1.012 to 1.032	?
Albumin.....	1 to 4 plus	Trace to 4 plus	4 plus
Microscopic observations	Hyaline and granular casts; white cells	Hyaline casts; white cells; red cells	Waxy casts
Blood:			
Hemoglobin content...	56 to 72 per cent	32 to 55 per cent	50 per cent
Erythrocytes.....	4,000,000 to 2,800,000	3,660,000 to 2,110,000	2,360,000
Leukocytes.....	14,000 to 40,000	7,100 to 12,300	13,100
Heart weight.....	220 Gm.	355 Gm.	480 Gm.
Kidney weights.....	285 and 290 Gm.	125 and 130 Gm.	140 Gm. each

explanation for the lack of hypertension as a constant observation in these cases is not clear.

In the accompanying table, it can be seen that the clinical diagnosis of this condition must be difficult. Frothingham, and Osler and McCrae stated that the diagnosis cannot be made except in cases in which amyloidosis is suspected. Save for the absence of hypertension, a diagnosis of chronic glomerulonephritis is justifiable, and in case 2 with hypertension this diagnosis would be as close as possible. In

24. Volhard, F., and Fahr, Theodore: Die brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

cases 1 and 2, a clinical diagnosis of chronic glomerulonephritis was made, while in case 3 the diagnosis was subacute glomerulonephritis. From a study of these cases, however, it would seem well to bear in mind the condition of amyloid kidney in the differential diagnosis of chronic nephritis. In the absence of hypertension, when the history reveals any reason to suspect amyloidosis, a clinical diagnosis of amyloid kidney with renal insufficiency would seem justifiable.

#### CONCLUSIONS

Amyloid kidney is one manifestation of a systemic disease and not a specific form of nephritis.

It is primarily a vascular disease that involves predominantly the glomeruli.

It can lead to renal insufficiency, and when this occurs the kidney is usually contracted, but in some instances renal insufficiency occurs in kidneys of normal size or even in enlarged kidneys.

The clinical symptoms and signs of an advanced amyloid kidney resemble those of chronic glomerulonephritis save for the fact that in amyloid kidney hypertension is the exception rather than the rule.

Amyloid, after being deposited in the kidney, may undergo some change which alters its staining characteristics.

# EXPERIMENTAL INFESTATION OF WHITE RATS WITH CYSTICERCUS FASCIOLARIS

MICROSCOPIC CHANGES IN LIVER, KIDNEY AND SPLEEN \*

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The present paper is the result of a study undertaken to see what differences in cellular structure occur in the liver, kidney and spleen of the white rat as a result of an infestation with *Cysticercus fasciolaris*, the larval stage of the cat tapeworm, *Taenia crassicolis*. Under the proper conditions, it is possible experimentally to introduce large numbers of *Cysticercus* cysts into the liver of the rat. Miller and Dawley<sup>1</sup> (1928) studied the grosser physiologic effects of the parasite on the host and made a special study of the progressive changes in the blood following infestation. The formation of the cysts and the grosser microscopic changes in the liver accompanying the process were described by Bullock and Curtis<sup>2</sup> (1924) in their work on the production of *Cysticercus* sarcoma. In the present study of the effects of *C. fasciolaris*, particular attention has been paid to the chondriosomes of the hepatic and renal cells of the host. These important cell constituents have been found to vary in form, size and number in many different functional and pathologic conditions. No attempt will be made to review here the extensive literature on this subject. Cowdry<sup>3</sup> (1924) gave an adequate account of the form and function of the chondriosomes, while Findlay<sup>4</sup> (1927) had an extensive bibliography on their relations to cellular pathology. In the case of the spleen, the matter of chief interest was the cellular structure of the organ, and not the structure of the individual cells.

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\* Submitted for publication, June 10, 1929.

\* The work on which this paper is based was done in the Department of Zoology at Washington University, St. Louis, during the spring and summer of 1928.

1. Miller, H. M., and Dawley, C. W.: An Experimental Study of Some Effects of *Cysticercus fasciolaris* Rud. on the White Rat, *J. Parasit.* **15**:87, 1928.

2. Bullock, F. D., and Curtis, M. R.: A Study of the Reactions of the Tissues of the Rat's Liver to the Larvae of *Taenia Crassicolis*, and the Histogenesis of *Cysticercus* Sarcoma, *J. Cancer Research* **8**:446, 1924.

3. Cowdry, E. V.: General Cytology, Chicago, University of Chicago Press, 1924.

4. Findlay, G. M.: Mitochondria and Cell Injury, *J. Roy. Micr. Soc.* **47**:258, 1927.

## MATERIALS AND METHODS

The rats used were of the pedigreed Wistar stock raised in this department. The method of infestation was that used by Miller and Dawley.<sup>1</sup> Mature proglottids of adult worms taken from the intestines of cats were teased in a physiologic solution of sodium chloride and the oncospheres fed to the rats, either by being mixed with their food or by means of a medicine dropper. The infested animals and the controls were kept under as nearly the same conditions as possible; in some cases, infested rats and their controls were kept in the same cage. The latter were always killed at the same time as the animals known to be infested.

All rats were killed either by cutting off the head with large scissors or by crushing the head with one blow of a hammer. Each rat was opened as quickly as possible after killing and small pieces of tissue were cut out with a razor and placed immediately in the fixing fluid. The same order of removal was practiced in all cases, namely: liver first, kidney next and spleen last.

The fixatives used were Champy's chromo-osmic fluid and Regaud's mixture of potassium dichromate and formaldehyde for preservation of chondriosomes, and Bouin's solution of picric acid and formaldehyde for ordinary cell structure. Paraffin sections, from 4 to 5 microns thick, or material fixed in Champy's and Regaud's fluids were stained with the original Altmann stain (anilin acid fuchsin-picric acid) or with the Bensley-Cowdry modification of this (anilin acid fuchsin-methyl green). Sections, from 6 to 8 microns thick, of material fixed in Bouin's solution were stained with Ehrlich's hematoxylin and eosin, Haidenhain's iron hematoxylin and acid fuchsin, and with Mallory's triple connective tissue stain. Of the two fixatives used for the preservation of chondriosomes, Regaud's mixture gave the clearer fixation, but Champy's solution, while it did not penetrate as well, showed the pathologic changes in the liver to best advantage, and at the same time served for the study of the fat content. The Mann-Kopsch and Kolatchev methods for the demonstration of the Golgi apparatus were uniformly unsuccessful. The arsenious acid-silver nitrate method of Golgi was successful in only two cases, and the results were mediocre. No differences worthy of note could be distinguished.

MICROSCOPIC CHANGES IN THE LIVER PRODUCED BY *C. FASCIOLARIS*

*Conditions in Normally Functioning Liver Cells.*—Before describing the differences between the liver cells of normal and those of infested rats, it will be necessary to make a few statements with regard to the chondriosomal content of the normal liver cell. Rathery<sup>5</sup> (1909) described the liver cell of the rabbit after using a chromo-osmic fixative. He found the chondriosomes in the granular form, mitochondria. Two types of cells were differentiated: one in which the mitochondria are scattered fairly uniformly in a homogeneous cytoplasm, which he called the "granular state"; and another, in which large clear spaces are found, forcing the cytoplasm which contains the mitochondria to the sides of the cell and around the nucleus and in between the spaces, the "clear state." The former he considered the normal condition. On the other hand, Noël<sup>6</sup> (1923), using Regaud's potassium dichromate-formaldehyde

5. Rathery, F.: La cellule hépatique normale, Arch. de méd. expér. et d'anat. path. **21**:50, 1909.

6. Noël, R.: Recherches histophysiologiques sur le cellule hépatique des Mammifères, Arch. d'anat. micr. **19**:1, 1923.

fixative, found the chondriosomes of the liver cells of the rat in the form of both granules and rods, or chondriocontes. He believed the clear state to be the normal state. The results of the present study confirm those of the authors mentioned, in that chondriosomes are found to be granular after chromo-osmic fixation, and both granular and rod-shaped after potassium dichromate-formaldehyde fixation (figs. 1 and 3). Cells of both clear and granular type are found. Both may be present in the liver of the same animal, either in approximately equal numbers or with one type predominating. In other cases, only one type of cell is found. This variation cannot be correlated with differences in fixation, as postulated by Rathery, nor with differences in the nutritional state of the animals, since both types seem to be normal.

In the present study, actively functioning hepatic cells of rats heavily infested with *C. fasciolaris* showed certain chondriosomal variations from the normal. There was a definite increase in the size of the chondriosomes in cells of infested animals, noticeable after both types of fixation (figs. 1 and 2; 3 and 4). In cells fixed with Regaud's potassium dichromate-formaldehyde, it was seen that a decrease in the number of chondriocontes had occurred as a result of the infestation (figs. 3 and 4). An attempt was made to count the chondriosomes in several cells of each liver in order to determine whether there had been an increase in the number of chondriosomes in the cells of the infested animals. Owing to certain technical difficulties, no numerical results are offered, but the general statement can be made that there is an increase in the number of chondriosomes per cell in the liver of an infested rat. These results point to an increased activity in the functioning liver cells of infested rats. The increased size of the chondriosomes, the change from chondriocontes to mitochondria and the increased number of chondriosomes are all well known evidences for an increased cell activity. The explanation is obvious; the destruction of large amounts of liver tissue by the growth of the cysts throws an increased burden on the remaining cells with a corresponding necessity for hyperfunction.

*Changes in Hepatic Cells under Pathologic Conditions.*—Bullock and Curtis<sup>2</sup> called attention to three pathologic conditions in the livers of rats infested with *C. fasciolaris*: (1) necrosis of liver cells, (2) pressure atrophy and (3) fatty infiltration. These have been investigated in the present study by the use of chondriosomal fixation and the staining of liver tissue from heavily infested rats. In addition, a fourth condition has been observed, which is assumed to be that of cellular hyperfunction.

As stated by Bullock and Curtis, necrosis occurs mainly during the early stages of the formation of the cyst, and to any great extent



only in a few cases. In the present work, the shortest time elapsing between infestation and the taking of tissue was nineteen days. In one of these cases, a slight necrosis was still visible, mainly in liver cells that had been included in the cyst wall, although a few such cells were also found at the edge of the cyst. These cells were vacuolar (fig. 6); the size of the vacuoles ranged from about that of a mitochondrion to about twice that size. It was evident that the vacuoles were the remains of mitochondria, for every gradation from normal mitochondria to full-sized vacuoles could be found. The former seemed to swell and gradually to lose their staining power, a few at a time, until the whole cell was full of vacuoles. Presumably, the cell then disintegrated. So far as is known, there has been no similar observation on the relation of mitochondria to the vacuoles of degeneration. Lewis<sup>7</sup> (1919) observed vacuolar degeneration in cells in tissue cultures, but the mitochondria did not seem to be involved. The results of the present study of cells in necrosis are also different from those obtained by Mayer, Rathery and Schaeffer<sup>8</sup> (1909, 1910) in their study on the autolysis of liver cells of the rabbit. These differences are probably to be explained on the basis that the mechanism of cell destruction in the one case is entirely different from that in the other.

The changes in the chondriosomes of cells undergoing pressure atrophy were slight. Such cells, found at the edges of the cysts, showed only those changes that have been described for normally functioning liver cells of infested animals; i.e., an increase in the number and the size of the chondriosomes and a tendency for the chondriocontes to give way to mitochondria.

In the livers of rats killed during the earlier stages of the infestation (at from nineteen to thirty days), the cysts were surrounded each by a more or less broad band of cells in which the mitochondria were enormously swollen, but retained their staining properties. In some cases, the mitochondria were even more deeply stained than normally. This resulted in a condition in which the cells were practically filled with large, brightly staining, red globules (fig. 5). There was a gradual transition from these cells to the normally functioning cells at the edge of the zone. So far as could be observed, there was no fusion of the globules such as that in autolysis as described by Mayer, Rathery and Schaeffer, nor did the cells tend to disintegrate, and the condition disappeared as the infestation proceeded. A similar condition in which

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7. Lewis, M. R.: Degeneration Granules and Vacuoles in the Fibroblasts of Chick Embryos Cultivated in Vitro, *Bull. Johns Hopkins Hosp.* **30**:81, 1919.

8. Mayer, A.; Rathery, F., and Schaeffer, G.: Lésions expérimentales des cellules du foie, *Compt. rend. Soc. de biol.* **67**:709, 1909; Lésions expérimentales de la cellule hépatique, *Arch. de méd. expér. et d'anat. path.* **22**:177, 1910.

the globules fused in autolysis of liver cells, was described by Dyson<sup>9</sup> (1912). However, the evidence seems to show that these cells do not go to pieces, but return to the normal condition after the infestation has proceeded for a time. The assumption has been made that this is a condition of intense hyperfunction on the part of cells surrounding the places where the greatest amount of tissue has been lost. Another explanation is suggested by the arrangement of these cells in a band about the cyst, namely, that a toxin is produced by the parasite, which diffuses out of the cyst and affects the cells, causing them to undergo this change. Miller and Dawley could not demonstrate any toxicity of the cyst fluid, nor has any such toxin ever been found or its effects on cells described. However, this is also a possible explanation.

The present study confirms the previous observation of Bullock and Curtis that a moderate fatty infiltration of the liver occurs in the earlier stages of the infestation. The globules of fat occurred in largest numbers around the central veins of the lobules and around the cysts. They were also numerous in the inner layer of the cyst wall. These droplets of fat occurred both in the sinusoids and in the liver cells themselves. In the latter case, an interesting condition was observed (fig. 7). The cells were normal with one exception: the nuclei stained as usual, and the chondriosomes stained with the same intensity as those of normally functioning cells; but with the appearance of fat in the cells, there was a corresponding decrease in the number of chondriosomes. There can be no doubt that the droplets were true fat and not lipoids. Both fats and lipoids were blackened by the osmic acid during the fixation with Champy's fluid, but, in the subsequent treatment of sections with 1 per cent potassium permanganate, the lipoids were decolorized immediately, while the fat was decolorized only after treatment for from ten to fifteen minutes followed by alcohol and xylene.

The decrease in the number of chondriosomes accompanying the appearance of fat in the cells raises the question as to whether there is a true fatty infiltration, or whether it may not be a fatty degeneration. The immense literature on the subjects of fatty infiltration and fatty degeneration has been adequately reviewed by Wells<sup>10</sup> (1925) and will not be reviewed here. The chief evidence for a fatty degeneration given by the present study was the disappearance of chondriosomes incidental to the appearance of fat. Several authors, notably Scott<sup>11</sup>

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9. Dyson, W.: The Staining of Granules in the Liver Cells Before and After Autolysis, *J. Path. & Bact.* **17**:12, 1912.

10. Wells, H. G.: *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1925.

11. Scott, W. J.: Experimental Mitochondrial Changes in the Pancreas in Phosphorus Poisoning, *Am. J. Anat.* **20**:237, 1916.



Fig. 2

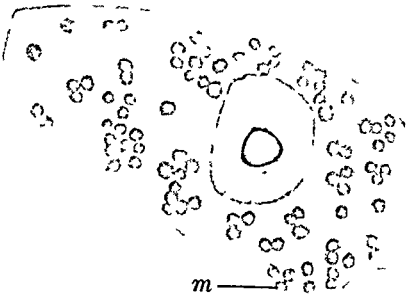


Fig. 1



Fig. 4

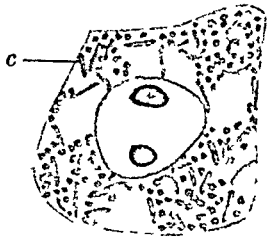


Fig. 3

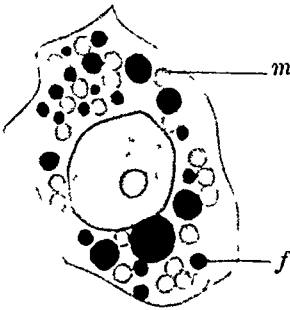


Fig. 7

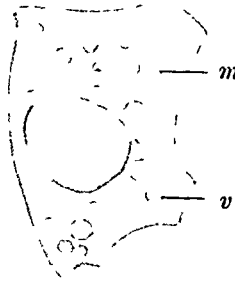


Fig. 6

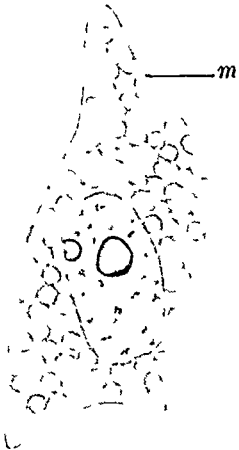


Fig. 5

## EXPLANATION OF PLATE

All figures were drawn with the aid of a camera lucida, using a Bausch and Lomb oil immersion lens and 10 $\times$  ocular. The original drawings were enlarged by one-fourth with the pantograph and were reduced to the original size in printing. Total magnification,  $\times$  1,250.

Abbreviations: *c*, chondriosomes; *f*, fat globules; *m*, mitochondria; *v*, vacuoles.

Fig. 1.—A normal liver cell in the granular state, of an uninfested rat weighing 205 Gm. The liver weighed 9 Gm. Champy fixation; stained with acid fuchsin-methyl green.

Fig. 2.—A normal liver cell in the granular state, of an infested rat weighing 190 Gm. The liver weighed 32 Gm. The cell shown is one taken nineteen days after the infestation of the rat. Champy fixation, stained with acid fuchsin-methyl green.

Fig. 3.—A normal liver cell in the clear state, of an uninfested rat weighing 145 Gm. The liver weighed 6 Gm. Regaud fixation, acid fuchsin-methyl green stain.

Fig. 4.—A normal liver cell in the clear state, of an infested rat weighing 272 Gm. The liver weighed 88 Gm. The cell shown was taken fifty-two days after infestation. Regaud fixation, acid fuchsin-methyl green stain. (Figures 3 and 4 are of the same magnification; it may be seen here that the chondriosomes in figure 4 are actually, as well as seemingly, larger than those in figure 3.)

Fig. 5.—An abnormal liver cell of the same rat as the cell in figure 2. Champy fixation, acid fuchsin-methyl green stain.

Fig. 6.—A vacuolar liver cell of the same rat as the cells in figures 2 and 5. Champy fixation, acid fuchsin-methyl green stain.

Fig. 7.—A liver cell with fat globules, of an infested rat weighing 140 Gm. The liver weighed 30 Gm. The cell was taken nineteen days after infestation. Champy fixation, acid fuchsin-picric acid stain.

(1916) and Noël<sup>6</sup> (1923), described the formation of fats from the chondriosomes, while other investigators, Hess and Saxl<sup>12</sup> (1910), Ignatowitsch<sup>13</sup> (1914) and Fischer and Hooker<sup>14</sup> (1917), stated their belief that fat is formed from the masked lipoids of the cell, which are probably the chondriosomes. On the other hand, the work of several others may be cited in favor of the view that this is a case of fatty infiltration. According to Lewis<sup>15</sup> (1918), when cells in tissue cultures form fat droplets, the chondriosomes are not involved. Munk<sup>16</sup> (1908) and Krontowski and Poleff<sup>17</sup> (1914) showed that fat may be formed in cells or taken up by them from the surrounding medium, and that the former process occurs only during autolysis and degeneration. In the present work, it was evident that the cells containing the fat were not degenerating, and so it would seem that these cells took up the fat from the sinusoids. It is probable that the disappearance of the mitochondria was due to the solvent action of the fat, since, as is known, the lipoids are fat-soluble. The author is therefore of the opinion that Bullock and Curtis were right in their description of the condition as a fatty infiltration.

As an explanation of the condition of fatty infiltration, two views may be presented. Fischer and Hooker<sup>14</sup> pointed out that fatty infiltration of the liver occurs as a result of an acidosis due to lowered oxidation. It seems likely that such a condition would occur in the livers of infested rats, since the presence of a large number of cysts occupying the end-branches of the portal veins (Bullock and Curtis) must lead to an interference with the circulation of the liver and result in a lowered oxidation of the cells. The other explanation is based on the work of Coope and Mottram<sup>18</sup> (1914), who found a fatty infiltration in the livers of female cats during pregnancy. Their explanation is that the liver, under the condition of heightened activity, can no longer metabolize the fat in the amounts supplied, so that it piles

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12. Hess, Leo, and Saxl, P.: Eiweissabbau und Zellverfettung, *Virchows Arch. f. path. Anat.* **202**:148, 1910.

13. Ignatowitsch, D.: La dégénérescence graisseuse "in vitro," *Compt. rend. Soc. de biol.* **76**:607, 1914.

14. Fischer, M. H., and Hooker, M. O.: *Fats and Fatty Degeneration*, New York, John Wiley & Sons, 1917.

15. Lewis, M. R.: The Formation of the Fat Droplets in Cells of Tissue Cultures, *Science* **48**:398, 1918.

16. Munk, F.: Ueber lipoide Degeneration, *Virchows Arch. f. path. Anat.* **194**:527, 1908.

17. Krontowski, A., and Poleff, L.: Ueber das Auftreten von lipoiden Substanzen in den Gewebs-kulturen und bei der Autolyse der entsprechenden Geweben, *Beitr. z. path. Anat. u. z. allg. Path.* **58**:407, 1914.

18. Coope, R., and Mottram, V. H.: Fatty Acid Infiltration of the Liver During Pregnancy and Lactation, *J. Physiol.* **49**:23, 1914.

up in the sinusoids of the organ. This explanation is as feasible as the former one; the evidence for a heightened activity in the liver cells of infested rats has been presented earlier in this paper. It seems unnecessary to choose between these two explanations; both are equally applicable to the present case, and probably both operate together.

#### MICROSCOPIC CHANGES IN THE KIDNEY

No constant cytologic differences could be observed between the kidney cells of normal and those of infested rats. This is rather surprising when one considers the close relationship existing between liver function and kidney function. It is still more surprising in view of the fact that large amounts of liver tissue were being destroyed and the products taken up by the blood, and the fact of the extra load thrown on the kidneys by the waste products of the parasite in the liver. The fact that no visible changes were found speaks against the theory that a toxin is formed by the parasite. According to Simonin<sup>19</sup> (1920), during chronic toxemia from verminous toxins, chronic nephritis is present, and the cells of the convoluted tubules of the kidney become greatly vacuolar. No such conditions could be observed in the present study, and the negative result must be taken as further indication of the fact that *C. fasciolaris* is a benign parasite (Miller and Dawley).

#### CHANGES IN THE CELLULAR CONTENT OF THE SPLEEN DUE TO INFESTATION WITH *C. FASCIOLARIS*

Comparison of sections of the spleens of normal with those of infested rats showed that there had been a great increase in the number of megakaryocytes in the infested animals. These cells are easily recognizable by virtue of their large size, lobed nuclei and granular cytoplasm staining lavender with hematoxylin and eosin after Bouin's fixation. That megakaryocytes are found normally in small numbers in the spleen of the rat has been asserted by De Kervily<sup>20</sup> (1912), who stated that the normal number may be as high as thirty per square millimeter. An attempt was made to determine the relative increase in number by actual count, using the following method:

The unit of measure taken was the number of megakaryocytes per field. Counts were made with the high-power objective and 10 $\times$  ocular, which gave a field of about 0.44 mm. diameter by measurement with a stage micrometer. The total number of fields per section and the total number of megakaryocytes were recorded for three sections each of the spleens of six infested rats and two controls. The

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19. Simonin, P.: Introduction à l'étude des toxines vermineuses, Nancy, Humbolt & Cie, 1920.

20. De Kervily, M.: Sur la présence de megakaryocytes dans la rate de plusieurs Mammifères adultes normaux, *Compt. rend. Soc. de biol.* **72**:34, 1912.

sections were of material fixed in Bouin's solution; they were 8 microns thick and stained with Ehrlich's hematoxylin and eosin. When there was any doubt as to the identity of the cell, it was not counted, which may account for the rather low number found in normal rats (compare with figure given by De Kervily<sup>20</sup>). The results are set forth in the accompanying table.

It may be seen from the table that all three factors, namely, the number of cysts present, their size and the duration of the infestation, are of importance in determining the increase in the number of megakaryocytes in the spleen. However, these three factors are not of equal importance; the size of the cysts and the duration of the infestation seem more important than the number of the cysts. For example, rat 7, with 6,030 cysts of 1 mm. diameter, showed a much smaller increase than rat 9, with 2,720 cysts of 2 mm. diameter, although the length of infestation was the same. It is also of interest to compare rats 8 and 160, in which the cysts were large and the duration great,

*Comparison of Normal and Infested Animals with Regard to the Number of Megakaryocytes in the Spleen*

Rat	Cysts	Diameter of Cysts, Mm.	Length of Infestation, Days	Total Count of Megakaryocytes in 3 Sections	Number of Fields in 3 Sections	Ratio of Megakaryocytes to Fields
3	....	..	..	1	191	.005
1	....	..	..	4	191	.021
7	6030	1	19	19	138	.138
160	1	8	.. *	43	288	.149
11	2160	2	24	62	213	.291
9	2720	2	19	108	145	.745
8	116	3-7	52	300	373	.804
12	3625	2	14	227	278	.817

\* Accidentally infested at some time previous to beginning experiment.

although the number of cysts was less, with the other rats of the series. However, the number of animals in the series was far too few to justify the drawing of any definite conclusions as to the relative importance of these three factors.

The significance of the increase in the number of megakaryocytes in the spleen of an infested rat is not clear. The function of the megakaryocytes was believed by Wright<sup>21</sup> (1906, 1910) to be the formation of thrombocytes, or blood platelets, and this work was confirmed by Bunting<sup>22</sup> (1909) and Downey<sup>23</sup> (1913). According to Bunting, a thrombocytosis is accompanied by an increase in the number of megakaryocytes in the bone-marrow. However, there is no evidence of a thrombocytosis in the case of infestations with *C. fasciolaris*, nor

21. Wright, J. H.: The Origin and Nature of the Blood Plates, Boston M. & S. J. **154**:643, 1906; The Histogenesis of the Blood Platelets, J. Morphol. **21**:263, 1910.

22. Bunting, C. H.: Blood Platelet and Megakaryocyte Reactions in the Rabbit, J. Exper. Med. **11**:541, 1909.

23. Downey, H.: The Origin of Blood Platelets, Folia Haemat. **15**:25, 1913.

could Miller and Dawley observe any significant difference in the clotting time of blood between infested rats and their controls. So far as can be determined from the literature, no observation similar to the present one has been made in the case of any other parasitic infestation. Donhauser<sup>24</sup> (1908) found megakaryocytes in the spleen of a patient with metaplasia, but no such condition is to be seen in the spleens of infested rats. It is of interest that Bunting<sup>25</sup> (1911) showed that the megakaryocytes increase in number in the bone-marrow of patients with Hodgkin's disease. However, the eosinophilia in Hodgkin's disease is local, and not general as shown for *C. fasciolaris* by Miller and Dawley. Such a parallelism is nevertheless not without obvious value in this case, for the etiology of Hodgkin's disease has never been satisfactorily determined. I believe that a study should be made of the megakaryocytes in a number of other parasitic diseases in order to determine whether this enormous increase is a general condition or one specific for the cysticercosis of the rat.

#### CONCLUSIONS

The liver cells of uninfested white rats may be in either the "clear" or "granular" state independent of the fixative used, and as far as can be ascertained, also independent of the nutritional state of the animal.

The chondriosomes of the liver cells of white rats may be in the form of granules (mitochondria) or of both granules and rods (chondriocontes), dependent on the type of fixative used; the former condition appears after fixation with chromo-osmic fluid, the latter after fixation with the potassium dichromate-formaldehyde mixture.

Functioning liver cells of white rats heavily infested with *Cysticercus fasciolaris* show the characteristic picture of increased activity, namely, an increase in the size and the number of the chondriosomes and a tendency for the chondriocontes to fragment into mitochondria.

In the necrosis of liver cells of infested rats occasionally accompanying the formation of the cysts, there is a gradual decrease in the number of mitochondria. These lose their staining properties and swell, becoming vacuoles, so that the entire cell just before disintegration is vacuolated.

Liver cells undergoing pressure atrophy show only those chondriosomal changes that are found in functioning liver cells of infested rats.

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24. Donhauser, J. L.: The Human Spleen as an Haematoplastic Organ, etc., J. Exper. Med. **10**:559, 1908.

25. Bunting, C. H.: Blood Platelets and Megakaryocytes in Hodgkin's Disease, Bull. Johns Hopkins Hosp. **22**:114, 1911.



In a more or less broad band of cells around each cyst in livers of infested rats there is observed a condition, with transition to the normally functioning cells, in which the mitochondria are intensely stained and extremely swollen so as to fill almost the entire cell. The assumption has been made that this is evidence of extreme hyperfunction, although it may possibly be evidence of the formation of a toxin in the cysts.

The observation of Bullock and Curtis that a fatty infiltration of the liver occurs in infested rats is confirmed by this work. The fat is found as globules around the centrolobular veins, around the cysts and in the inner layer of the cysts. Fat is found both in the sinusoids and in the cells, in the latter case with a corresponding decrease in the number of mitochondria, so that this condition might be considered as evidence for a fatty degeneration rather than a fatty infiltration. However, from the fact that these cells containing fat show no signs of degeneration, the conclusion is reached that the process is one of true infiltration, with taking up of fat by the cells with solution of the mitochondria in the fat. Two explanations are offered for the fatty infiltration, one on the basis of impeded circulation with a resulting lowered oxidation and acidosis, the other on the basis of heightened activity of the organ.

No constant cytologic changes could be observed in the kidney cells of infested rats, which opposes the theory of toxin formation.

In the spleens of infested rats there is observable an increase in the number of megakaryocytes per field of high power magnification. No explanation of the condition can be offered, but in this and in the presence of an eosinophilia, the cysticercosis of the rat resembles Hodgkin's disease in man.

## TRAUMATIC PORENCEPHALY \*

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Porencephaly is usually defined as a funnel-shaped defect of the brain which extends from the surface of a hemisphere close to or into the lateral ventricle. The defect is covered by a membrane of varying thickness and is filled with a clear, colorless fluid; thus, on external examination, it appears as a cyst.

In the first descriptions, which date from more than a century ago,<sup>1</sup> these defects were considered as malformations, an explanation at first also given by Heschl,<sup>2</sup> who in 1859 introduced the term porencephaly. While Heschl later changed his explanation in favor of circulatory disturbances, particularly a lack in the blood supply of the involved regions of the brain, Schattenberg,<sup>3</sup> von Kahlden<sup>4</sup> and Ziehem maintained the dysontogenic origin. Heschl's vascular theory was taken over by Kundrat,<sup>5</sup> Bourneville and Schwartz<sup>6</sup> and many other investigators. A number of authors discussed the significance of traumatic and inflammatory changes.

The theory that has the greatest weight of evidence is undoubtedly that which emphasizes the importance of trauma. Defects of the brain similar to those which are apparently congenital may develop in later life from areas of traumatic, hemorrhagic softening (Boettger,<sup>7</sup> von

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\* Submitted for publication, June 12, 1929.

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1. The early literature on porencephaly is reviewed by Schuette, E.: *Die pathologische Anatomie der Porencephalie*, *Centralbl. f. allg. Path. u. path. Anat.* **13**:633, 1902.

2. Heschl, R.: *Gehirndefect und Hydrocephalus*, *Vrtljschr. f. d. prakt. Heilk.* **61**:61, 1859.

3. Schattenberg, A.: *Ueber einen umfangreichen porencephalischen Defekt des Gehirnes bei einem Erwachsenen*, *Beitr. z. path. Anat. u. z. allg. Path.* **5**:121, 1889.

4. Von Kahlden: *Ueber Porencephalie*, *Beitr. z. path. Anat. u. z. allg. Path.* **18**:2, 1895.

5. Kundrat, H.: *Die Porencephalie. Eine anatomische Studie*, Graz, 1882.

6. Bourneville and Schwartz: *Nouvelle contribution à l'étude de la porencéphalie et pseudo-porencéphalie*, *Progrès méd.* **8**:37, 1898.

7. Boettger, quoted from Schroer: *Zur Kenntnis der traumatischen Porencephalie*, *Virchows Arch. f. path. Anat.* **262**:144, 1926.

Kahlden, Kaufmann,<sup>8</sup> Kennard,<sup>9</sup> Kopp,<sup>10</sup> Landouzy and Labbé,<sup>11</sup> LeCount and Semmarek<sup>12</sup> (case II of their series), Ponfick,<sup>13</sup> Schroer,<sup>14</sup> Struchlik-Sirotow<sup>15</sup> and others). Von Kahlden distinguished these acquired forms from the true congenital porencephaly, a differentiation which had to be given up because it was impossible to draw a borderline between true and acquired porencephaly (Beyer<sup>16</sup>). Siegmund<sup>17</sup> called any defect of the brain from an aseptic necrosis porencephaly.

The trauma that leads to a porencephaly may affect the brain while the fetus still is in the uterus (Seitz,<sup>18</sup> Kikuth<sup>19</sup>) or it may occur during birth, in infancy or in later life. The most common cause is undoubtedly the trauma occurring at birth (Frangenheim,<sup>20</sup> d'Hollander and Schmidt,<sup>21</sup> Siegmund, Schwartz<sup>22</sup> and others). In the history of cases of porencephaly there is a striking frequency of prematurity, prolonged labor and instrumental delivery. The investigations of Siegmund and, in particular, of Schwartz have revealed a continuous chain of changes from the areas of loosening and softening of the brain substance and the hemorrhages as immediate sequels of the birth trauma to the fully developed porencephalic cysts. In addition to the direct action of the

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8. Kaufmann, E.: *Lehrbuch der speziellen pathologischen Anatomie*, Berlin-Leipzig, Vereinigung Wissenschaftlicher Verleger 1922, vol. 2, p. 1441.

9. Kennard, K. S.: Case Report: Primary Tumor of the Heart. Porencephalus, New York State J. Med. **21**:346, 1921.

10. Kopp, J.: Ein Fall von Porencephalo-Hydrocephalia traumatica unilateralis permagna, Deutsche Ztschr. f. Chir. **116**:226, 1912.

11. Landouzy and Labbé, M.: Les porencéphalies traumatiques, Presse méd. **7**:66, 1899.

12. LeCount, E. R., and Semerak, S. B.: Porencephaly, Arch. Neurol. & Psychiat. **14**:365 (Sept.) 1925.

13. Ponfick, E.: Ueber Hirncysten und Porencephalie, Centralbl. f. allg. Path. u. path. Anat. **8**:858, 1897.

14. Schroer (footnote 7).

15. Struchlik-Sirotow, S.: Zur Frage über die sekundäre Degeneration der Pyramidenbahnen bei Porencephalie, Arch. f. Psychiat. **54**:1056, 1914.

16. Beyer, E.: Zur Lehre der Porencephalie, Neurol. Centralbl. **15**:823, 1896.

17. Siegmund, H.: Die Entstehung von Porencephalien und Sklerosen aus geburtstraumatischen Hirnschädigungen, Virchows Arch. f. path. Anat. **241**:237, 1923.

18. Seitz, L.: Ueber die durch intra-uterine Gehirnhämorrhagien entstandenen Gehirndefekte und die Encephalitis congenita, Arch. f. Gynäk. **83**:701, 1907.

19. Kikuth, H.: Beitrag zur Genese und Klinik der Porencephalie, Jahrb. f. Kinderh. **111**:112, 1926.

20. Frangenheim, P.: Aetiologie und Behandlung der Cephalhydrocele traumatica, Arch. f. klin. Chir. **152**:676, 1928.

21. D'Hollander and de Schmidt, P.: Contribution à l'étude anatomo-clinique de la sclérose lobaire, Arch. internat. de méd. expér. **1**:1, 1924.

22. Schwartz, Philip: Die traumatischen Schädigungen des Zentralnervensystems durch die Geburt. Anatomische Untersuchungen, Ergebn. d. inn. Med. u. Kinderh. **31**:165, 1927.

trauma on the brain, circulatory disturbances in the large veins of the brain from a backing up of the blood in the sinuses of the dura mater are of great importance.

Several authors have tried to associate the porencephaly with inflammatory processes in the brain and leptomeningi (Babonneix,<sup>23</sup> Ball and Anger,<sup>24</sup> Globus,<sup>25</sup> Henkel,<sup>26</sup> LeCount and Semerak, Sironi,<sup>27</sup> Stenström,<sup>28</sup> Winterode and Lewis<sup>29</sup>). Syphilis has been blamed for it by Henkel, LeCount and Semerak (case III) and by Delore and Pic.<sup>30</sup> It has to be kept in mind, however, that the presence of inflammatory changes in a brain with a porencephalic defect does not necessarily mean that the inflammation has produced the defect. For instance, in the case of tuberculous porencephaly published by Winterode and Lewis, it is much more likely that the child had first porencephaly and later tuberculous encephalitis than that the latter caused the defect. It is well known that the cerebral lesions from birth trauma, glial scars and cysts remain points of diminished resistance in which at a later time complicating changes are apt to occur (Schwartz). These complicating changes account, at least in part, for the fact that the first clinical manifestations of the porencephaly may appear months or even years after birth or that the symptoms may be aggravated with progressing age.

The case of porencephaly that is the subject of this paper is of interest not only because the traumatic origin seems to be well proved, but also because microscopically the brain shows changes some of which are still a matter of discussion.

#### REPORT OF A CASE

*Clinical History.*—A white American woman, aged 22, was brought to the Cook County Hospital in such an exhausted condition that the history could not

23. Babonneix, L., and Lhermitte, J.: Étude histologique des plaques fibromyéliniques du cortex cérébral et de la pia mère dans un cas de microcéphalie avec porencéphaly, *Compt. rend Soc. de biol.* **88**:1014, 1923.

24. Ball, V., and Anger, L.: Encéphalopathies atrophiques du jeune âge. Porencéphalie vraie unilatérale et idiotie chez un chat, *J. de méd. vétérin. et de zootechn.* **72**:397, 1926.

25. Globus, J. H.: A Contribution to the Histopathology of Porencephalus, *Arch. Neurol. & Psychiat.* **6**:652 (Dec.) 1921.

26. Henkel, K.: Polioencephalitis mit Ausgang in Porencephalie, *Ann. d. Krankenhäuser zu München* **96**:127, 1899.

27. Sironi, L.: Contributo clinico ed anatomo-pathologico allo studio delle eterotopie midollari, *Riv. di clin. pediat.* **19**:705, 1922.

28. Stenström, N.: Arachnoiditis hemorrhagica together with porencephalia, *Acta med. Scandinav.* **56**:591, 1922.

29. Winterode, R. P., and Lewis, N. D. C.: A Case of Porencephalic Defect Associated with Tuberculous Encephalitis, *Arch. Neurol. & Psychiat.* **10**:304 (Sept.) 1923.

30. Delore, M. P., and Pic, M.: Maladie polykystique du foie et des reins. Porencéphalie avec hémiplégie infantile, *Lyon méd.* **60**:489, 1928.

be taken. Every four or five minutes she had seizures which started with a tonic convulsion lasting for from five to ten seconds. During this convulsion, the head was drawn backward and the face was turned to the right. The right arm was extended, and the left arm was flexed. The legs were extended, and there was a plantar flexion of the feet. The tonic stage was followed by clonic convulsions, which involved the entire body, except the left side of the face, and lasted for about forty seconds. There was nystagmus with a quick component to the left. After the attacks, the eyes moved aimlessly and at times deviated laterally. The breathing during the attacks was stertorous, and following the attacks it was labored. The pulse was fast and of good quality. The patient made signs to tell that she had a visual aura and a choking sensation before the onset of the convulsions.

From the patient's sister, the following history was obtained. The patient's birth was spontaneous and rapid. In the course of the excitement that followed the birth, the baby was dropped to the floor from a height of about 30 inches (80 cm.). It fell on its head and remained unconscious for several hours, so that those present thought that it was dead. Immediately after regaining consciousness, it began to have convulsions. The godmother, who was present at the delivery, stated that at birth the baby was normal.

The child developed normally, except for frequent attacks of headache followed by fainting spells. These attacks persisted after the patient became mature. They were of short duration and occurred at intervals varying from one to three months. After her marriage, fourteen months previous to her admission to the hospital, the attacks became more and more severe, completely exhausting the patient, and she died from bronchopneumonia.

*Autopsy.*—On external examination, the head showed nothing abnormal. There were several scars on the lateral margin of the tongue. The skull was symmetrical, and the dura mater was smooth and tightly stretched over the posterior half of the left hemisphere.

The brain weighed 1,305 Gm. The left occipital lobe was the site of a cyst which occupied the convex surface, extending posteriorly from a line connecting the anterior occipital sulcus with the parieto-occipital fissure to the pole of the lobe. On the median and basal aspect, the occipital convolutions were preserved, but appeared flattened. The cyst was covered by a thin, transparent membrane, which seemed to be the direct continuation of the leptomeningi. The sagittal diameter of the cyst was 5 cm., the transverse diameter 4 cm. and the vertical diameter 3.5 cm. The content was a clear, colorless fluid, which escaped when the medulla oblongata was severed so that the cyst collapsed.

A sagittal section through the middle of the left hemisphere (fig. 1) revealed that the cyst had resulted from a funnel-shaped defect in the brain substance, which communicated with the posterior horn of the left lateral ventricle. The narrow end of the funnel measured 10 mm. in diameter and opened into the ventricle. The membrane on the surface contained several irregular, moderately firm, pale yellowish-gray areas, from 3 to 6 mm. in diameter and from 0.5 to 1 mm. in thickness. At the edge of the defect, the membrane passed into the leptomeningi, but a thin layer of grayish-white brain tissue was attached to its internal surface as it became free, and gradually merged with it.

The lateral wall of the defect was formed by smooth white brain substance. A delicate network of branched blood vessels extended from the lateral wall through the cavity to the surface membrane. The ependyma of the ventricles was smooth, and there was a marked dilatation of the posterior horn of the left lateral ventricle.

Coronal sections through the other parts of the brain did not reveal anything abnormal.

The rest of the observations made at autopsy were as follows: confluent bronchopneumonia of both lower pulmonary lobes; cloudy swelling of the liver, with areas of fatty degeneration; acute tumor of the spleen; solitary cyst, 4 by 5 by 2.5 cm. in diameter, in the upper pole of the left kidney; menstruating uterus; small follicular cysts in both ovaries; and a hemorrhagic corpus luteum in the right ovary.

*Microscopic Observations in the Brain.*—From the white matter of the occipital lobe, the cyst was separated by a membrane of dense fibrillar glia. The membrane was about 0.1 mm. thick and did not contain any nerve fibers. It was covered



Fig. 1.—A porencephalic cyst in the left occipital lobe communicating with the posterior horn of the lateral ventricle. The drawing is after the specimen, which was preserved in Kaiserling solution.

on the inside by a very low cuboidal epithelium. The parietal gliosis continued into the lateral ventricle. The convolutions that took part in walling off the cyst were narrow and tapered into the membrane that formed the roof of the cyst (fig. 2). Nowhere did the gray matter border on the cyst, but the latter was covered on the inside by a thin layer of medullary nerve fibers and glia. The cyto-architecture of the cortex was preserved only in the part adjacent to the valley of the convolution, while toward the surface the ganglion cells became more and more scanty and lost their arrangement to parallel horizontal layers. Some of the ganglion cells were shrunk and surrounded by neuronophages. The tapering part of the convolution was completely devoid of ganglion cells, their place being taken by fibrillar glia and medullary nerve fibers, which ran in

various directions and showed varicose swellings. Where the cortex passed into the surface membrane, the cyst possessed a distinct cuboidal epithelium (fig. 2 *E*).

The free membrane on the surface of the cyst had an average thickness of 220 microns. It consisted of two layers, an outer one of connective tissue with blood vessels and single mononuclear cells and an inner one made up of fibrillar glia. The inner layer varied in thickness and in places swelled up to form plaques, which were as much as 800 microns thick. The glia contained only a few nuclei and capillary blood vessels. The plaques were more cellular, the cells accumulating in the outer third. They had round nuclei with a finely granular chromatin net and centrally located nucleoli, which took the basic stain. Many of these cells

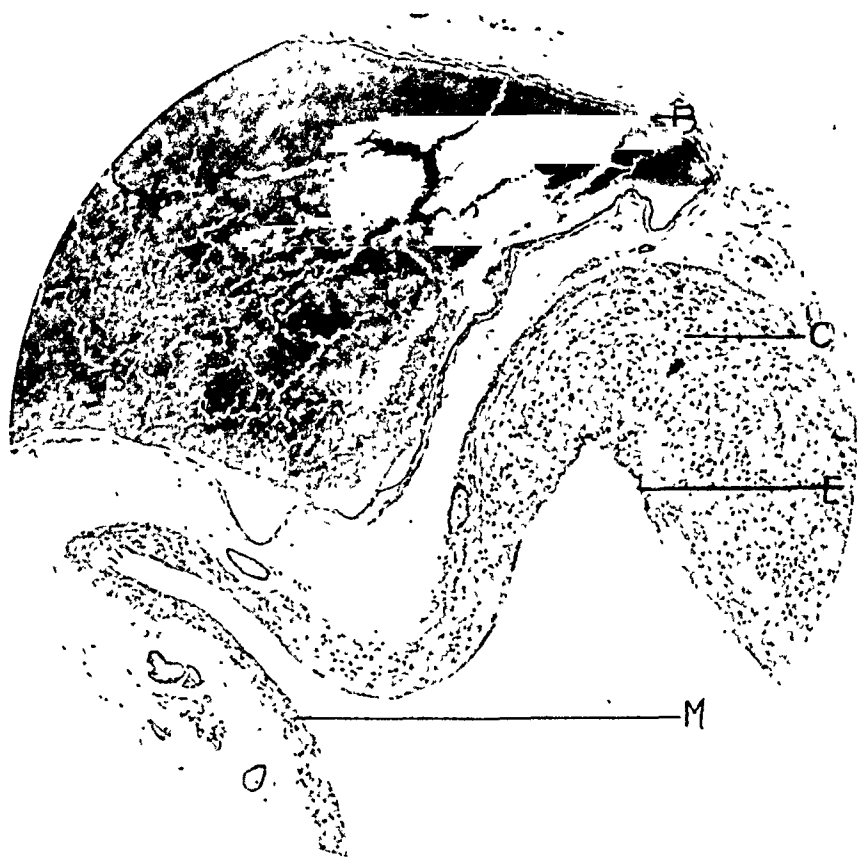


Fig. 2.—A photomicrograph illustrating the relations of the glial part of the porencephalic membrane to the lateral wall of the cyst. Note the tapering of the cortex (*C*) into the membrane (*M*) and the distinct epithelial lining (*E*). The dark area in the upper half of the field (*B*) is a dilated meningeal vein. The material was fixed with a diluted solution of formaldehyde, U. S. P. (1:10). The section was stained with hemalum-eosin; magnification, 60 times.

were filled with dark brown and yellowish-brown pigment granules (fig. 3). With Turnbull's reaction for iron, the dark brown granules stained deep blue, while the yellowish-brown granules either remained unstained or appeared a light green. Outside the plaques there was only a little pigment. Nerve cells could not be detected nor did specific stains (Bielschowsky, Alzheimer, Weigert-Pal, Kultzinsky, Spielmeier) demonstrate any nerve fibers. Here and there one found small spherical bodies that gave the microchemical reaction of calcium.

Bundles of glia fibrils, from 40 to 150 microns thick, extended from the glial part of the membrane into the outer zone of connective tissue. In transverse sections, these bundles appeared as whorls surrounded by a capsule of connective tissue. This ingrowth of glia into the mesenchyma was most marked at the edges of the cyst where the bundles reached a length of 2.5 mm., crossed the sulcus and extended to the vertex of the next convolution.

The mesenchyma part of the membrane continued as pia and arachnoidea over the adjacent convolutions. Where it filled the sulcus that separated the cyst from the rest of the brain, it contained accumulations of large oval cells, many of which had engulfed dark brown pigment granules.

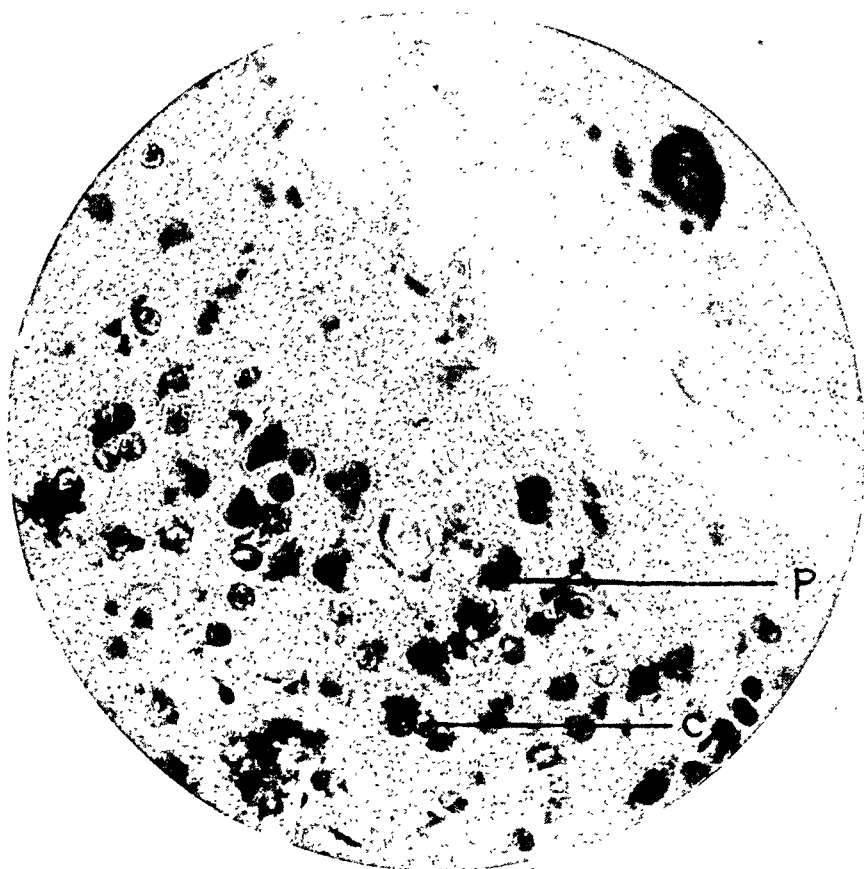


Fig. 3.—Deposits of blood pigment (*P*) in the large glia cells (*C*) of a plaque-like thickening of the membrane. The technic is outlined in the legend for figure 2; magnification, 450 times.

In the convolutions adjacent to the defect, which on gross examination appeared normal, cone-shaped, sharply circumscribed areas of gliosis were found (fig. 4). They were located in the vertex of the convolutions and extended through the entire thickness of the ganglion cell layers, the base of the cone fusing with the molecular layer, and the apex extending into the medulla. The areas measured 3 mm. in length and 1 mm. in depth, and, in addition to fibrillar glia, contained loose bundles of medullary nerve fibers, which crossed each other in various directions and were connected with the fibers of the central part of the convolution. There were no nerve cells in these areas.



Sections were taken from the central and paracentral convolutions, the temporal lobes, the insula Reili, the corpus callosum, the choroid plexus, the pons, the corpora quadrigemina, the pedunculi cerebri, the cerebellum, the nucleus caudatus, the thalamus opticus, the putamen, the globus pallidus and the nucleus lentiformis. They did not reveal any abnormalities, except a moderate thickening of the leptomeninges over the cerebral hemispheres.

#### COMMENT

The trauma from which the patient had suffered immediately after she was born seemed to be the most reasonable explanation for the

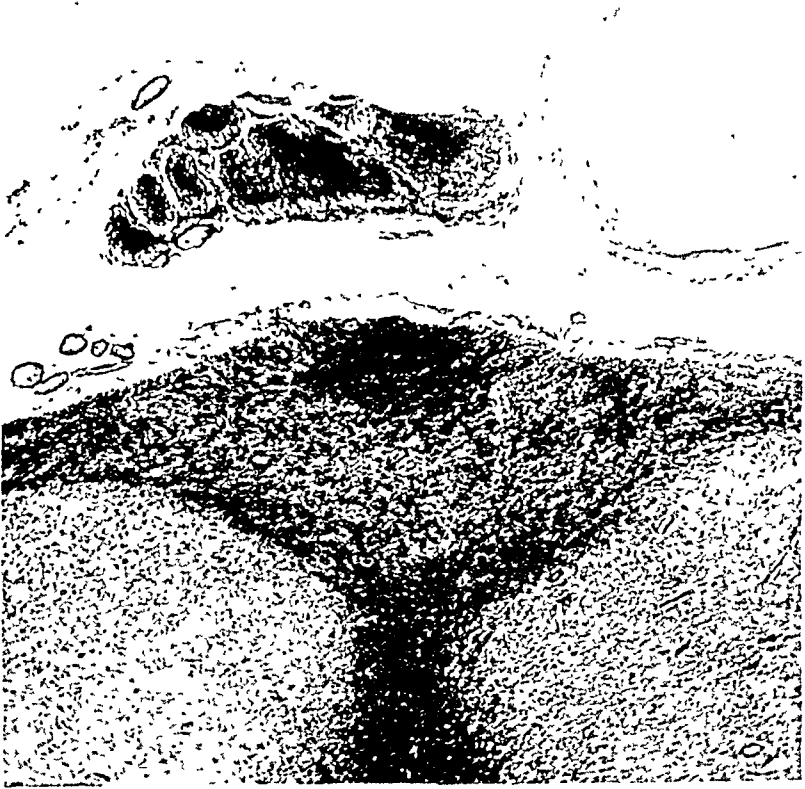


Fig. 4.—A cone-shaped area of gliosis in the cortex of a convolution adjacent to the defect. Above the area is a transverse section through a bundle of glia tissue distinctly separated from the cortex of the brain. In serial sections, this bundle could be traced to the glial part of the porencephalic membrane. The material was fixed with a diluted solution of formaldehyde, U. S. P. (1:10). Mallory's stain (phosphotungstic hematoxylin) was used; magnification, 60 times.

large cyst of the occipital lobe. The birth was spontaneous and rapid, and though precipitate birth does not seldom lead to injuries of the brain, the close association of the first clinical manifestations with the accident speaks strongly in favor of the postnatal origin of the initial lesion. The cyst showed the macroscopic and microscopic picture that is typical of porencephaly. The most common location of porencephaly

is the central convolutions and the insula of Reil, the parietal region being especially exposed to birth injuries. In about 14 per cent of the cases, the occipital lobe is found affected (Siegmund). Porencephaly from birth trauma is frequently bilateral and is often combined with other structural changes of the brain, such as microgyria, nodular thickenings of the ependyma and glial scars in the cerebral cortex and central ganglia. In the present case, the defect was unilateral.

The literature on porencephaly contains the records of a number of cases in which the defect could be traced to a trauma in the postnatal life. The age at which the trauma had occurred varied greatly. Thus Ponfick<sup>13</sup> reported a case of porencephaly in a man aged 23, who at the age of 3 years had been hit on the head by the vanes of a windmill. Kopp's<sup>10</sup> patient, who was successfully operated on for a large porencephalic cyst when he was 16, had fallen from the third floor when he was 3. Struchlik-Sirotow's<sup>15</sup> patient, a man aged 37, who had a large cyst in the region of the left central convolutions, had been run over by a car at the age of 7. In Boettger's<sup>7</sup> case, the accident had occurred when the patient was 17 (with death at 66); in Schroer's<sup>14</sup> case, at the age of 48 with death at 58, and in von Kahlden's,<sup>4</sup> at the age of 45 (with death at 50).

The question will arise whether there are differences in the reactive changes of the central nervous tissue, as evidenced by the structure of the wall of the cyst, between the defects which form in the immature brain and those which develop after the organ has attained its morphologic maturity. The studies of Spatz<sup>31</sup> seem to suggest such differences. Spatz compared the effect of sewerage of the spinal cord in new-born with that in adult rabbits, and found that in the immature central nervous tissue there was a rapid liquefaction of the traumatized area and a quick removal of the debris, while the reactive changes of the glia and especially of the mesenchyma were insignificant. In the adult, glial and mesenchyma proliferation predominated over the liquefaction and led to scars composed of glia and connective tissue. Cysts formed in the mature central nervous system had a distinct wall that gradually passed into the adjacent normal tissue, whereas porencephalic cysts originating in fetal life, during birth or in early infancy had a thin wall that was sharply separated from the normal brain. The immature brain, he thought, possesses a great adaptability, which permits destructions so extensive that if they occurred in the brain after it reached maturity they would be incompatible with life. He concluded that it is the differentiation of the medullary tissue that determines the form of reaction.

Spatz's conclusions were criticized by Schwartz. Schwartz, to whom great credit is due for calling attention to the tremendous

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31. Spatz, H.: Ueber eine besondere Reaktionsweise des unreifen Zentralnervengewebes, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 53:363, 1920.

importance of injuries of the brain at birth, pointed out that Spatz performed his experiments on new-born rabbits, in which the central nervous system is much less mature than even in the youngest premature infant. Many injuries of the immature brain do not lead to cysts, but to glial scars. If the large porencephalic defects show a lack of reactive changes, it is due to their bordering on regions of the brain with different functional properties and a different vascular supply. In destructive processes of the adult brain a similar lack of reaction is observed, if they involve a functional and structural unit of the brain, for instance, the centrum semiovale. In typical porencephaly, however, as in the case reported, the fact that the mesenchyma does not take part in the walling off of the defect remains an outstanding feature and it has yet to be proved that the same indifference of the connective tissue to acute lesions of the brain may also occur in the mature organ.

Communication with the ventricles is found in both forms of porencephaly, in the early ones as well as in those acquired in later life. The initial lesion may extend into the ventricle, or a cyst at first separated from it by a thin membrane may later break into the ventricle by gradual growth from an increasing accumulation of fluid, since the thin wall permits expansion.

Three histologic observations may be discussed in detail; namely, the structure of the membrane that covers the defect, the deposits of blood pigment in this membrane and the adjacent leptomeningi, and the cortical areas composed of glia and medullary nerve fibers in the convolutions near the cyst.

Most of the investigators who have studied microscopically the porencephalic membrane have emphasized that a thin layer of nervous tissue was attached to the inside of the thickened leptomeningi. Siegmund believed that the porencephalic cyst never borders directly on mesenchyma tissue, but that it is always separated from it by a layer of brain tissue. Langhans,<sup>32</sup> who studied the membrane of a cyst operated on by Kocher, found on the surface sclerosed and vascular connective tissue while the rest was made up of a loose fibrillar tissue resembling glia. In the case observed by Frensdorf,<sup>33</sup> the membrane contained glia and medullary fibers. Bornhaupt<sup>34</sup> and Delore and Pic observed, in the glia, cells that looked like nerve cells. Seitz spoke of a layer of brain tissue of varying thickness, and Kopp described connective tissue and glia. In my case, the porencephalic membrane

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32. Langhans, quoted from Kopp (footnote 10).

33. Frensdorf: Fall von Porencephalie und Ulegyrie (Narbenbildung in der Rinde) auf vaskulärer Basis, Verhandl. d. Irrenärzte Niedersachsens und Westphalens, Session of May 5, 1923.

34. Bornhaupt, L.: Hirncyste des rechten Seitenventrikels operativ geheilt, Zentralbl. f. Chir. 45:404, 1918.

contained only glia. Nerve cells and nerve fibers could not be demonstrated.

It seems that the glial part of the membrane is the remnant of the plexiform layer of the cortex, the other layers of the cortex and the medullary tissue of the convolutions and of the centrum semiovale being replaced by the cyst. According to Schwartz, the different layers of the cortex possess a certain independence from each other, which explains why the plexiform layer may remain when the other parts of the cortex are destroyed by hemorrhage or softening.

There exists another lesion of the brain resulting from injuries at birth, which, too, is often associated with large cysts on the surface or the base of the hemispheres, namely, lobar atrophy (lobar sclerosis). The pathogenesis of these cysts, however, is different from that of the porencephalic cysts, from which they should be distinguished. While in porencephaly it is a softening and liquefaction of the entire brain substance that leads to the formation of the cyst, in lobar atrophy the initial lesion is a loosening of the cortical and medullary tissue with a more or less complete destruction of the nerve fibers and ganglion cells followed by proliferation of the glia, sclerosis and shrinking (Schwartz). The shrinking of circumscribed, often large, areas of the brain produces depressions on the surface of the hemispheres, which are filled by cysts. The cysts contain a clear fluid and, on superficial examination, resemble porencephalic cysts. They are located, however, between the leptomeninges, the arachnoid membrane bridging the defect, while the pia mater is attached to the shrunken convolutions. In the external membrane of these cysts, I have not found any glia tissue, which I think is an important difference between the porencephalic cysts and the cysts over the atrophic parts of the brain in lobar atrophy.

In the porencephalic membrane, I have described bundles of glia extending from the ectodermic part into the leptomeningi. This ingrowth of glia into mesenchyma has been repeatedly observed. Globus saw it in a case of porencephaly with encephalitic changes. In a baby, aged 15 months, with porencephaly and micro-encephaly, Babonneix and Lhermitte<sup>28</sup> found dense plaques rich in medullary nerve fibers, which were located in the thickened pia mater and were distinctly separated from the cortex of the brain. In the case under discussion, the bundles of glia in the leptomeningi did not contain any nerve fibers.

Many of the reports on porencephaly mention a brownish pigmentation in and about the defect. This pigmentation was observed by the early investigators (Heschl, Rogers,<sup>35</sup> Birch-Hirschfeld,<sup>36</sup> Chiari<sup>37</sup>

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35. Roger: Ueber Porencephalie, Inaugural Dissertation, Erlangen, 1866.

36. Birch-Hirschfeld, F. V.: Ueber einen Fall von Hirndefekt infolge von Hydrops septi pellucidi, Arch. f. Heilk. 6:1, 1867.

37. Chiari, H.: Aus der Prosektur des St. Anna Kinderspitals in Wien, Jahrb. f. Kinderh. 15:330, 1880.

and others) and was sometimes considered proof of the traumatic origin of the defect. In my case, there were deposits of iron-containing and iron-free pigment in the plaques of the membrane and in the meningi adjacent to the cyst. Is this pigment a remnant of the hemorrhages caused by the trauma immediately after birth? It is hardly possible that blood pigment would be stored over so long a period of time, and another explanation seems to be more likely. In the introduction, I mentioned that the lesions of the brain from birth injuries remain points of diminished resistance in which later circulatory disturbances are apt to occur. Such circulatory disturbances may lead to hemorrhages months or even years after the injury. It is undoubtedly from these late hemorrhages that the pigmentation of the porencephalic cyst is derived.

Relatively recent small hemorrhages into the leptomeningi also account for the cellular accumulations in the meningi near the cyst. It is well known that extravasations of blood into the meningi cause a proliferation of the local histiocytes, which engulf the free red cells and their debris, transforming them into pigment.

Recently I studied the brain of a premature child, 7 months of age, who since birth had been suffering from a stiffness of the neck and of the back. This stiffness diminished, later to return with increased intensity. At necropsy, recent and old hemorrhages were found about the frontal lobes, the convolutions of which were narrow and separated by deep sulci. There was an extensive calcification of both suprarenal cortices. The microscopic examination of the brain revealed circumscribed areas of gliosis in the cortex of the frontal convolutions and in the upper part of the thalami optici. In the latter location there were numerous calcified ganglion cells. About the scars in the thalami optici there were recent hemorrhages surrounding dilated capillaries and venules.

The cortical areas of gliosis were of the same microscopic structure as were those in the case of porencephaly. There was a dense network of fibrillar glia containing thin medullary nerve fibers that were connected with the medulla of the convolutions. These areas resembled the "plaques fibro-myeliniques" described by Vogt and Vogt,<sup>38</sup> who found them frequently in the cortex of normal brains, in which they were so small and scanty as to cause no functional disturbances, being a mere incidental observation. In his studies on the myelinization of the cerebral cortex, Goichi<sup>39</sup> observed in the frontal gyri of two infants, aged 6 and 8 months, circumscribed areas of premature myelinization.

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38. Vogt, O., and Vogt, C.: *Zur Lehre der Erkrankungen des striären Systems*, J. f. Psychol. u. Neurol. **25**:633, 1920.

39. Goichi, Hirako: *Ueber Myelinisation in der Grosshirnrinde*, Schweiz. Arch. f. Neurol. u. Psychiat. **9**:275, 1921.

Goichi explained these foci on the basis of a locally increased blood supply, following von Monakow's conception of the correlation between vascularization and the development of the medullary sheaths.

In their case of porencephaly referred to in a preceding chapter, Babonneix and Lhermitte emphasized the presence in the cerebral cortex of well developed plaques of glia and medullary fibers. This observation and the cases that I have discussed seem to support an explanation first given by Schwartz, namely, that the "plaques fibro-myeliniques" may result from circumscribed areas of loosening of the cortical tissue caused by injuries of the immature organ. It is possible that the increased vascularization during the organization that follows the loosening of the brain substance accounts for the local overgrowth of medullary fibers. An excessive ingrowth of medullary fibers sometimes is also observed in the central ganglia, especially in the corpus striatum, giving rise to a peculiar change in the structure of the gray matter, the so-called "état marbre" (status marmoratus of Vogt and Vogt).

#### SUMMARY

A case of porencephaly in a woman, aged 22, is reported, which illustrates the great importance of the trauma in the etiology of this rare and interesting lesion. The trauma occurred immediately after birth and in its action on the brain could therefore be compared with the injuries that occur during birth. The histologic observations are discussed, especially in connection with the question of the reparatory processes in the immature central nervous tissue.

# EXTRADURAL LIPOMA OF THE SPINAL CANAL \*

J. A. KASPER, M.D.

AND

A. COWAN, M.D.

DETROIT

Extradural spinal lipoma is comparatively uncommon. Stookey,<sup>1</sup> in reviewing the literature to 1926, was able to find reports of only nine cases. He referred to a report by Chapelle<sup>2</sup> as being the first description of this type of tumor. In a recent report on a series of 179 extradural spinal tumors, Elsberg<sup>3</sup> recorded only one example of lipoma.

Being a benign tumor of soft consistence, lipoma presents a difficulty in roentgenologic diagnosis. This probably accounts for its infrequent recognition. It may be present without symptoms, unless it grows to a great size; then it produces pressure on the cord (Chapelle,<sup>2</sup> Obré,<sup>4</sup> Elsberg<sup>3</sup>).

For these reasons, and particularly because of an unusual clinical course, the present case is considered of sufficient interest to be reported.

## REPORT OF CASE

*History.*—R. D., a white boy, aged 6, was brought to this hospital to the pavilion for patients with meningitis during the recent epidemic of meningococcus meningitis in this region. His family physician had made a diagnosis of "suspected meningitis." At the time of admission, the temperature was 102.4 F. (rectal); the pulse rate was 120, and the respiration rate 32 per minute. He was irritable and irrational.

The onset of the present illness occurred four days before his admission to the hospital. The illness began with fever and sore throat. Two days after the onset, the patient vomited and complained of headache.

The past history was negative. Previous to the present illness the boy was in good health.

*Physical Examination.*—The positive observations were redness of the throat, an indefinite Babinski sign and exaggerated knee reflexes. No abnormal signs

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\* Submitted for publication, Sept. 5, 1929.

\* From the Pathological Laboratory and the Division of Communicable Diseases, Herman Kiefer Hospital, Department of Health.

1. Stookey, B.: Intradural Spinal Lipoma, Arch. Neurol. & Psychiat. **18**:16 (July) 1927.

2. Chapelle: Extradurales Lipôme, Bull. Soc. anat. **22**:6, 1847; quoted by Stookey.

3. Elsberg, C. A.: Extradural Spinal Tumors, Surg. Gynec. Obst. **46**:1, 1928.

4. Obré: Lipoma of the Meninges. Tr. Path. Soc. London **3**:248, 1852; quoted by Stookey.

were discovered in the chest. A spinal puncture was done, and 10 cc. of clear fluid was obtained. This was under slightly increased pressure and was followed by blood.

Examination of the spinal fluid showed a slight globulin reaction. Fehling's reaction was positive. No bacteria were found on direct smear or culture.

The observations did not warrant a positive diagnosis of meningitis, but the child was considered to be in a critical condition. He continued to be irrational and six hours after admission became cyanotic, and the respirations were labored. He became progressively weaker, and expired thirteen hours after admission.

*Autopsy.*—Autopsy was performed seven hours after death. Only the important observations are recorded.

The pupils were equal and regular, measuring 4 mm. in diameter. The sclerae were clear. In cutting through the skull below the occipitoparietal suture, the dura was cut, and immediately dark fluid blood began to flow out. This was collected in a basin, and the amount was estimated to be between 200 and 250 cc. When the calvarium was removed, the source of this blood was found to be in the spinal canal. The meningeal vessels were filled with blood. These were intact, as were the sinuses. There was no fracture in the skull. The pia and the arachnoid were transparent over the entire brain. No exudate was apparent. The brain was deep pink, moderately dry and firm. On section, the cortex of the cerebrum was found to be somewhat swollen. The cerebral capillaries were rather prominent. Perivascular extravasation of blood could not be found about any of them. The ventricles contained clear fluid. The spinal cord was exposed by removing the vertebral laminae. On the posterior surface of the dura were two masses of firmly adherent, dark pink, soft, friable substance which could not be removed en masse. The upper of these masses was in the region between the second cervical and the eighth dorsal vertebra. The lower was between the third lumbar and the second sacral vertebra. At the level of the fourth lumbar vertebra was clotted blood. Extravasated blood was also found within and around the extradural tumor. Where the needle for spinal puncture had entered through the dura, clotted blood was found on the inner surface. Reflection of the dura showed the cord to be slightly blood tinged. The tumor mass apparently had filled the space between the dura and the posterior wall of the spinal canal because the removed laminae contained it. It was firmly attached in the depressions between them. The other observation of importance was that of gray hepatization of the upper lobe of the right lung.

The anatomic diagnosis was pneumonia of the right upper lobe; hemorrhage into the spinal canal, and extradural glioma or lipoma.

*Microscopic Examination.*—Spinal Tumor: Several sections from different portions revealed fat tissue with moderately large vessels, which were filled with blood. There was rather extensive extravasation of blood into the mass of fat. A large blood clot was present on the external surface of the mass in one section. A section containing dura showed the fat tissue to be in close approximation on one surface. The opposite surface was smooth.

Cerebrum: Moderate edema was present throughout. The peripheral portion of the cortex showed slight necrosis. The pia was normal. No exudate was found in the arachnoid space. There was diffuse cerebral capillary dilatation and engorgement.

Right Lung: All alveolar capillaries were prominent and engorged. Most of the alveoli were filled with leukocytes, chiefly polymorphonuclears. All other alveoli contained thin fluid with few leukocytes and some fibrin.



The histologic diagnosis was extradural lipoma with hemorrhage; acute congestion of the cerebrum, and lobar pneumonia of the right lung.

*Roentgen Examination.*—The removed laminae containing the tumor were shown by x-ray to be normal. The study was made in two planes.

#### COMMENT

In reviewing the clinical course in this case, an explanation of the symptoms can be ventured on the basis of the anatomic observations. The irritability and the irrational state of the patient can be explained as having been due to a cerebral irritation of the nature of a meningism, caused by the toxemia resulting from the infection in the right lung.

The terminal cyanosis and respiratory distress were in all probability due to the intracranial pressure which was caused by the hemorrhage into the spinal canal following the spinal puncture.

Lipoma in the spinal canal often has its origin in the fat which is present about the vertebrae and even if this is located external to the canal,<sup>5</sup> penetration between the vertebrae may take place. The case which Elsberg<sup>3</sup> reported was of this type, since it was associated with multiple lipomatosis.

The chief interest evoked by the clinical course in this case is in the fact that a lipoma, which under ordinary conditions would be of little importance, has to be recognized as an indirect cause of sudden death following the employment of a valuable aid in diagnosis, namely, spinal puncture.

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5. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1919, p. 424.

# THE ISSUES AT STAKE IN THE GRADING OF TUMORS \*

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To me, as to most pathologists, has often come the desire to classify the material coming to my hands, as much for my own benefit as for that of others similarly interested. This has been particularly true of tumors.

The recent developments and revivals in the literature of the systems of so-called "grading" of carcinomas naturally intensified the original urge. I began to classify the 890 carcinomas of the breast available to me, and soon reached the appalling number of 500 different types; it became evident that such refinements (?) of analysis would lead to the absurd (?) result of 890 types of carcinoma in 890 breasts.

This study, together with that of tumors of other organs, again brought out the well known fact that there is as yet no adequate definition of a tumor. The only one which begins to satisfy is the total contents of a good monograph on malignant growths. Even this is inadequate, for until the biology of tumors is known, no definition can be inclusive.

This situation tends to restrict one to classifying tumors solely as "benign" or "malignant," and with knowledge of the later history of patients, obtained from a follow-up service, one must mentally hedge in this in some cases.

In view of the prominence occupied by tumor grading and my own experience with it, it seemed that the time had come for another examination into its rationale:

I have chosen to do this by first presenting the facts emerging from an investigation of the material collected over many years here at the Lankenau Hospital, and then discussing their significance in terms of tumor grading.

One hundred consecutive cases of carcinoma of the breast, dating from September, 1920, were taken for study. One hundred and five were necessary to complete the list, for in five cases the follow-up records were incomplete. It is clear that in order to judge of the validity of tumor grading the later history of the patient from whom the specimen was taken is essential.

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\* Submitted for publication, June 10, 1929.

\* From the Research Institute of the Lankenau Hospital.

\* This paper and the articles by Hammett and Ingleby, which were published in the October issue, and complete references to which will be found in this article, are supplementary and complementary to each other.

THE MANY VARIABLES THAT HELP TO DETERMINE THE  
HISTOLOGIC CHARACTER OF CARCINOMA

The first matter to be considered is the histologic character of the tissue removed. The ideas in regard to this almost choke the literature, which has recently been well reviewed by Plaut.<sup>1</sup>

In table 1, I have given the histologic pictures presented by each of my 100 specimens. From these, it is evident that a great diversity is exhibited. Every experienced pathologist knows that what is true of carcinoma of the breast is true of carcinoma of other organs, the differences being equally impressive when details are sought. So results

TABLE 1.—*The Histologic Pictures of Tumor as Determined in Specimens of Carcinoma of the Breast from 100 Patients*

	Dead of Metastasis (61)		Dead of Other Causes (18)		Living with Recurrence (4)		Living and Well (17)	
	Per- centage	Actual Fig- ures	Per- centage	Actual Fig- ures	Per- centage	Actual Fig- ures	Per- centage	Actual Fig- ures
Small cells . . . . .	29	18	33	6	..	0	23	4
Large cells.....	81	50	77	14	75	3	47	8
Nerosis: Sparse....	29	18	5	1	50	2	6	1
Massive. . . . .	14	9	33	6	..	0	..	0
Small nests: Loose....	24	15	5	1	..	0	17	3
Confined. . . . .	21	15	39	7	25	1	17	3
Large nests: Loose....	18	11	11	2	25	1	6	1
Confined.. . . .	39	24	39	7	..	0	17	3
Angular nests.....	11	7	5	1	..	0	17	3
Rounded nests . . . . .	2	1	5	1	..	0	..	0
Thin streaks. . . . .	47	29	27	5	75	3	53	9
Thick streaks . . . . .	36	22	22	4	25	1	35	6
Stroma:								
Fibrous, cells; Sparse . .	19	12	16	3	25	1	6	1
Profuse . . . . .	13	8	5	1	..	0	..	0
Acute... . . . .	28	17	16	3	25	1	6	1
Chronic . . . . .	24	15	11	2	25	1	11	2
Thrombosis: Lymph vessels . .	34	21	22	4	50	2	17	3
Blood vessels... . . .	6	4	..	0	25	1	..	0
Metastasis: Alike.....	34	21	14	3	50	2	11	2
Denser . . . . .	24	15	11	2	..	0	17	3
Looser.. . . .	..	0	..	0	..	0	..	0
Unlike . . . . .	5	3	..	0	..	0	..	0

from the analysis of these carcinomas of the breast are applicable to tumors in general.

What is it that determines the differences?

*Cell Size.*—The cell size is dependent on at least four factors: (1) the kind of cells, i. e., epithelial and their derivatives, etc.; (2) the structural environment, i. e., compression by dense tissue or freedom for expansion in loose; (3) the chemical environment, i. e., nutrition, toxic products, etc., and (4) the reproductive activity. Hammett<sup>2</sup> showed that cell size is inversely proportional to the rate of cell pro-

1. Plaut, A.: The Relation Between the Histologic Picture and the Prognosis of Tumors, Arch. Path. 3:240 (Feb.) 1927.

2. Hammett, F. S.: Cell Division and Cell Growth in Size, Protoplasma, to be published.

liferation. The coefficient of correlation in the meristem of root tips of *Zea mays* is  $-0.577 - 0.075$ .

On the biologic basis, then, small cells should be and are considered more "malignant" than large. But here the difficulty enters that small cells may result from lack of room to grow, or compression, and might not, indeed, represent a high rate of proliferation.

The omission of the state of the nucleus from this analysis is purposeful. The usual methods of taking the specimen and the way it is handled prior to fixation preclude the obtaining of any valid index of nuclear activity as of the time at removal. But even if one could obtain ideally fixed and stained preparations, who has time or opportunity to study serial sections of the tumors engulfing one from a busy surgical clinic? Besides, they would be of only one instant in the life of the carcinoma, i. e., when it was removed.

*Architecture.*—The architecture of the growth is dependent on at least eleven factors. The first four are the same as those influencing cell size. In addition, there are: (5) the adhesive property of the cells, which determines whether they stick together in larger or smaller nests, sheets or streaks; (6) the "erosive" power of the growth, as when a tumor eats away bone; (7) the "invasive" power of the cells as they insinuate themselves throughout the contiguous tissue of the host—this may be counteracted by compression exerted by the surrounding tissues or by their relative impenetrability; (8) the vascularity, i. e., the abundance or sparseness of blood and lymph channels and their size—included in this might be the relative amount of duct spaces; (9) organization factors, i. e., those which cause the growths to appear in discrete forms like ducts, acini, etc., as in adenocarcinoma; (10) secondary changes of all types, i. e., degeneration, necrosis, hemorrhage, hyalinization, calcification, pseudocysts and the formation of specific by-products of cellular activity, such as mucus; and (11) the architecture and the secondary changes in the surrounding tissue.

*Stroma Reaction.*—The reaction of the stroma depends on at least three factors: (1) the organ or the tissue in which the tumor is growing; (2) the physiologic state of the organ or the tissue in which the tumor is growing, and (3) the secondary changes in the tumor itself.

I found, as did Greenough<sup>3</sup> and others,<sup>4</sup> that cellular infiltration is particularly correlated with the degree of necrosis and degeneration in the tumor, and not with the hypothetical "resistance" to the growth as determined by the end-results.

3. Greenough, R. B.: Varying Degrees of Malignancy in Cancer of the Breast, *J. Cancer Research* 9:453, 1925.

4. Hueper, W. C.: Carcinomas of the Uterine Cervix, *Arch. Path.* 6:1064 (Dec.) 1928.

One should dispose of the idea that the stroma reaction is due to the cancer cell as a "foreign body," for the reaction is not specific to degenerating or necrotic cancer cells, but is found wherever disintegration of tissue takes place, and is not found in cancer save when necrosis is in progress. On the biologic basis the concept is unsound also. For if those who have made a study of tumors are correct in their belief that the cells of most carcinomas are derivatives of preexisting normal cells, the most obvious point of difference is lack of restriction to multiplication and cancer cells are, therefore, not "foreign bodies." For to consider the cancer cell as a "foreign body" would be to believe that it is a biologic "sport" or mutation. No evidence for this is available. That the carcinoma cell undergoes degeneration and then becomes toxic as does any other cell under like conditions is, therefore, more readily explained on environmental than on hereditary grounds, at least at present. Certainly, if it were a foreign body, immunologic reactions should be demonstrable, but thus far all attempts in this direction have been unsuccessful. Nevertheless, the interesting results of Gruskin<sup>5</sup> may be consulted, in which the embryonic cell concept is supported, and the "immunologic" work of Lumsden<sup>6</sup> on sarcoma in rats; sarcoma in rats is, however, far different from carcinoma in man.

Finally, as far as this phase is concerned, I cannot bring myself to the belief that carcinomas obey their own rules and have nothing to do with the laws that govern normal growth. All my sympathies are with attempts to discover the laws of normal growth in the belief that abnormal growths behave differently only in detail. This subject is discussed at length by Hammett.<sup>7</sup>

Considering the breast as a physiologic structure, I find the following factors to be of prime importance: Signs of functional strivings are present even at birth. From the onset of puberty until the menopause (and after) the breasts of women are never physiologically quiescent. Nearly every woman at practically every menstrual cycle is aware of this fact. The most potent stimulus to activity of the breast is, of course, pregnancy. The anatomic reactions are hypertrophy and hyperplasia of the gland tissue and regression of the connective tissue. There is ever-increasing budding of the terminal ends of the ducts and

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5. Gruskin, B.: A Serum Test for the Diagnosis of Cancer Based on a New Theory of Etiology, *Am. J. M. Sc.* **177**:479, 1929.

6. Lumsden, T.: Chemotherapy by Means of Vaccine Treatment and Immunity, *Rep. Internat. Conference on Cancer, London, 1928*, p. 216.

7. Hammett, F. S.: An Interpretation of Malignant Growth Based on the Chemistry of Cell Division, *Arch. Path.* **8**:575, 1929. For a discussion from the morphologic point of view, see Müller, Heinrich: Eine einheitliche Erklärung für die im menschlichen Körper vorkommenden geweblichen Neubildungen, *Virchows Arch. f. path. Anat.* **269**:105, 1928; Die histologische Übereinstimmung zwischen Epithelregeneration und Krebsbildung, *Ztschr. f. Krebsforsch.* **28**:383, 1929.

a coincident disappearance of connective tissue, probably to make room. When lactation is interrupted the reverse occurs: the connective tissue undergoes hyperplasia and the glandular tissue disappears, until finally the perilobular connective tissue again surrounds small lobules at the ends of the ducts.

It is now fairly well established that the menstrual changes are the same as those of pregnancy, only less in degree. This means that in the normal breast there is a constant reciprocal growth and recession of epithelium and connective tissue.<sup>8</sup>

These normal physiologic changes of menstruation cannot help but be important factors in the determination of the histologic picture in mammary carcinoma. They also must be significant factors in determining the type of growth that occurs.

Considerable degrees of fibroblast reaction may, indeed, not be, as is often stated, a "defense" reaction on the part of the adjacent tissues, but can be the normal menstrual hyperplasias. Also, in the normal breast, small "round" cells are in the picture of every lobule. Most of these are not inflammatory in origin, but are epithelial cells in some stage of normal progression or regression. They look like inflammatory cells at first glance, and hence may be misinterpreted as a "defense" reaction.

Furthermore, it is well known biologically that cell reproduction can take place at almost any stage of the life of the cell. That is, the two cells that result from division of a mother cell can immediately undergo division without waiting to grow. Further, old and adult cells are still capable of dividing to repair wounds under the proper stimulus. Hence, this property may well be a factor in the production of the diversity of anatomic types of carcinoma exhibited in this or any other similar material.

Thus, when certain epithelial cells become carcinomatous, they may conceivably begin to divide at any stage they happen to be in. If the parent cells of a carcinoma are full grown and have reached the stage of forming an acinus, or duct, the daughter cells may also be large and form an adenocarcinoma. If, on the other hand, the mother cell gives rise to daughter cells before full differentiation, the carcinoma will be composed of smaller cells not arranged in architecturally definite form.

The pathologic fact that adenocarcinomas of the breast occur less frequently than other types, may, on grounds of cell heredity, be due to the fact that the mature stage of the cells in the breast lobule is of shorter duration than the preceding and succeeding phases of cell differ-

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8. McFarland, J.: Residual Lactation Acini in the Female Breast, *Arch. Surg.* 5:1 (July) 1922. Reimann, Stanley P.: Kaufmann's Pathology [tr.], Philadelphia, P. Blakiston's Son & Company, 1929, p. 1766.

entiation. Besides, the stimulus to grow is closer to immature cells just divided (as in menstrual hyperplasia) than when they are fully grown.

Furthermore, the gross spread of a carcinoma of the breast is undoubtedly influenced by the physiologic state of the organ. In the first place, the breast is periodically stimulated to grow, and it is possible that this normal stimulus to cell proliferation exerts an additional effect on the division of the carcinoma cells. On the other hand, the inhibitors of cell reproduction, which normally restrict untoward menstrual hyperplasia, may retard the proliferation of the carcinomatous cells. Thus, the growth picture would vary according to the respective stimuli arising from the normal physiologic processes.

Then during the epithelial hyperplastic stage, the ducts tend to be more dilated and to increase in number. This affords increased opportunity for a spread of the malignant growth in these channels. The disappearance of some fibrous tissue at this stage and the general loosening of the tissues yields a similar opportunity for spread in other channels. During the fibrous hyperplastic stage, when the ducts tend to become constricted, and the tissues tighten up again, hindrance to spread is increased. The coincident changes in vascularity obviously provide at times a more, and at times a less, plentiful supply of materials for growth.<sup>9</sup>

#### OUTCOME OF ATTEMPTS TO GRADE ONE HUNDRED CARCINOMAS ON HISTOLOGIC OBSERVATIONS ALONE

In the foregoing paragraphs, I have outlined the more significant factors concerned in the production of the histologic picture which the pathologist sees under the microscope and attempts to interpret. The implications to be derived from this analysis will be better brought out after I have given the results of my experiences in the grading of tumors.

As stated before, the validity of the grading of a tumor rests on the confirmation of the prognosis from the section by the subsequent history of the patient.

I therefore first graded the 100 specimens according to their relative apparent malignancy and then compared the prognoses with the actual outcomes. Naturally, the end-results were not known to me from the follow-up records until the classification had been completed. In the grading, small cell size, much mitosis and little degeneration were taken as unfavorable. In the architecture, streaks, small nests, large nests, sheets and mucoid and adeno types were taken as of

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9. Ingleby, Helen: Anatomic Study of a Case of Carcinoma of the Breast Giving Details of This Process, *Arch. Path.* 8:653, 1929.

decreasing order of malignancy. Excessive lymphatic thrombosis was recorded. Vascular thrombosis was considered unfavorable.

After careful analysis, I concluded that the group could be divided into three classes: The first, or grade 1, should be dead in twelve months; the second, or grade 2, should be dead in twenty-four months, and the third, or grade 3, should be alive and well. The relation between predictions and actual outcomes may be summarized as follows: Class 1—correct 6 times, incorrect 9 times. Class 2—correct 35 times, incorrect 31 times. Class 3—correct 9 times, incorrect 10 times. Total—correct 50 times, incorrect 50 times.

It therefore seems as if the histologic criteria commonly used for the prognosis of relative malignancy are inadequate.

Not satisfied with this result because of the insistence of various workers on the validity of tumor grading, I tried another line of attack. In my 100 cases, seventeen of the patients had remained living and well. I therefore took the seventeen slides of the specimens from these living patients, mixed them with seventeen slides from patients who had died of metastases within eight months of operation, and attempted to tell which was which. My efforts to distinguish the two sets resulted in 54 per cent correct, and 46 per cent incorrect, guesses.

Not wishing to rely on my own judgment entirely, I asked and obtained the willing assistance of four experienced pathologists of Philadelphia in doing the same experiment. The highest score was 57 per cent correct, and 43 per cent incorrect, guesses. Mathematically speaking, since the guesses were 48, 52, 53, 54 and 57 per cent correct, the average correctness was 53 per cent, which is 3 per cent above the 50 per cent corresponding to pure chance, a dangerously narrow margin, certainly too small for practical use from the point of view of the individual patient.

Since in this group of 100 patients, seventeen were living and well, four were living with recurrences and presumably would soon die and sixty-one had died of metastases, in any random selection of slides (representing patients as they come for operation) the chances are 4 in 5 for selecting the slide of a patient who will die. If I use my judgment (i. e., examine the slide chosen at random and grade it), the chance of my being correct either way is slightly better than 50-50, i. e., pure chance.

As a matter of interest, I cite three specific cases.

CASE 1.—The radical operation for carcinoma of the breast was performed by Dr. John B. Deaver on Mrs. F. S. in 1921, five weeks after the discovery of a lump in the breast. There was no clinical or pathologic axillary involvement. The tumor was about 1 inch (2.5 cm.) from the nipple, in the lower outer quadrant, fairly superficial, in a fatty breast. It was of the spherical type with no visible crablike prolongations, and only 1.5 cm. in diameter. The cells stained



well, appeared "differentiated" and had a tendency toward "adeno" formation, with few mitoses. No reaction was present in the stroma. An excellent prognosis! The patient remained perfectly well for fifty-five months; then several dozen tiny, shotlike nodules appeared on either side of the length of the scar on the chest wall, extending outward in both directions for about 6 inches (15.24 cm.). These nodules grew at about the same rate at first, until a number lower down on the chest wall, where there was considerable tissue between the skin and the ribs, soon outstripped the others. Above, where a minimum of subcutaneous tissue intervened between the skin and the ribs, the rate of growth of the nodules was much less rapid. Intensive treatment with x-rays and radium made no impression on the growth. Seventy months after the operation the patient died of loss of liver function from replacement by carcinoma.

Were the breast nodules a new tumor, or a number of different new tumors, or a growth of fragments remaining from the old tumor?

Histologic sections of four nodules showed identity as to carcinoma but dissimilarity as to detail. Several were so like the original, removed five years before, that without the labels it was impossible to separate them. They could be divided about as follows: The first was like the original growth. The second showed much more infiltration of lymphocytes, plasma cells, polyblasts, etc., but there was considerable necrobiosis of the smaller, more deeply stained cells. In the third, the cells were larger with more cytoplasm. They were arranged in fairly large nests, closely packed and growing into fatty areolar tissue. In the fourth specimen, some cells grew in smaller nests, but mostly they appeared in thin streaks through the interstices of a denser connective tissue, i. e., scar. The cells themselves were smaller and denser, and contained few mitoses.

Histologically, it was not a new tumor, or a number of different new tumors, but a recurrence of the original growth; i. e., at the time of operation, the tumor already existed beyond the lines of incision for amputation.

What determined the differences in the rate of growth of the separate nodules? Both the gross and the microscopic appearances suggested strongly that the environment was the significant factor. The tumors in the looser tissue grew the faster.

Evidence consistent with the idea of environment as a determining factor is also present in the next case.

CASE 2.—The radical operation for carcinoma of the breast was performed on Mrs. H. in 1923. The tumor was of the crablike infiltrating type. The breast itself was fatty. In some heavy bands of connective tissue, the tumor was composed of thin streaks and little nests of small, compressed, dark-staining cells: 0.5 cm. beyond, the tumor grew into the fat of the breast in larger nests, which were close together, with the cells larger and better stained, and having nuclei larger with more mitoses. Here, not only the architecture but also the cellular detail was influenced by the environment. The prognosis from the histologic section was bad, and was correct; for the patient died shortly after of metastases.

The third case illustrates the inability to prognosticate the extent and distribution of tumor fragments from the microscopic examination of the specimen removed.

CASE 3.—The radical operation for removal of carcinoma of the breast was performed on Mrs. H. in 1924. All the data, including the histologic picture of the growth removed, pointed to a good prognosis. One month later she returned

complaining of "lumps" all over her body. The palpating hand found literally hundreds of small, shotlike, subcutaneous nodules everywhere in the arms, legs, back, abdomen, chest, neck and scalp. She died two months later of what might in full justice be termed "general carcinoma." All the nodules grew (but naturally not at the same rate). Certainly, this "accident" could not have been anticipated from the section of the tumor.

#### COMMENT AND CONCLUSIONS

It is obvious from cases 1, 2 and 3 that if one is to make a prognosis at all, the presence or absence and the situation of secondary deposits are important. Every experienced pathologist has seen the liver practically destroyed by metastases, the patient dying from loss of liver function without help from metastases elsewhere. Clearly, an accurate prognosis depends, also, on a prediction of where the tumor will go.

From the British reports and others,<sup>10</sup> there seems little doubt that the radical operation is attended with more favorable end-results; that the chances of survival are in inverse proportion to the length of time the tumor has existed, and that the presence of metastases is decidedly unfavorable.

As a matter of record, I am giving tables showing these relations in my 100 cases. They are too few for statistical analysis, but may be added to the data of others, so that a large total can be collected for final analysis at some future time. I will be glad to furnish any available details that are not included in the tables.

The facts recorded in this paper demonstrate what reason should make clear, that it is futile to attempt to decide, from an examination of a section of the tumor, what will happen to a patient with cancer.

In the first place, even if one agrees that the inherent capacity for growth differs from tumor to tumor, it must be acknowledged that the factors that condition this difference vary in different persons, not only in their relative, but also in their absolute, influence. One cannot escape the general biologic fact that the form of expression of heredity is molded by the bars of environment. A few of the many environmental variables affecting the form expressed by the carcinomatous growth have already been cited in previous paragraphs. These variables, both structural and physiologic, cannot be controlled, for they are pre-determined by the organ and the organism in which the growth is taking place. Neither can they be anticipated, nor can their respective values in the total picture be allocated, for one never knows what place they

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10. Rep. Brit. Ministry of Health, London, no. 28. Lane-Claypon, J. E.: *Cancer of the Breast and Its Surgical Treatment*, *ibid.*, no. 32; *Further Report on Cancer of the Breast*, no. 34. Leeds: *Late Results of Operation for Cancer of the Breast*, *ibid.* Lee, B. J., and Stubenbord, J. G.: *Clinical Index of Malignancy for Carcinoma of the Breast*, *Surg. Gynec. Obst.* **47**:812, 1928.

TABLE 2.—*The Factor of Time in Cases of Patients Operated on for Carcinoma and Dying of Metastasis*

Ages	Time of Death, Months	Time Between Consultation and Operation	Ages	Time of Death, Months	Time Between Consultation and Operation
51	24	12 months	36	13	3 months
50	45	5 months	42	14	12 months
39	10	3 months	57	21	1 week
45	12	6 months	47	21	10 months
61	37	6 months	38	21	6 months
50	17	7 months	48	31	9 months
55	37	12 months	57	13	5 months
36	7	4 months	51	26	18 months
41	12	5 months	48	8	4 months
65	14	2 weeks	44	12	6 months
51	30	4 months	45	4	10 days
59	39	6 weeks	42	30	2 months
59	6	24 months	52	17	24 months
45	24	5 months	28	18	11 months
45	72	2 months	41	21	10 days
30	16	12 months	34	13	13 months
70	16	24 months	42	9	At once
52	20	12 months	48	6	3 months
35	69	5 weeks	50	36	2 months
31	9	3 months	41	54	3 months
46	9	3 months	76	4	20 years
55	14	4 months	50	23	1 week
45	4	7 months	38	22	3 months
46	20	30 months	36	6	5 months
45	69	5 months	43	28	3 months
52	20	1 month	58	4	24 months
39	10	9 months	36	6	36 months
39	15	5 months	48	15	At once
30	8	6 months	40	3	4 years
55	20	1 month	47	21	2 months
			42	13	6 months

TABLE 3.—*The Factor of Time in Cases of Patients Operated on for Carcinoma and Dying from Causes Other than the Carcinoma*

Ages	Time of Death, Months	Time Between Consultation and Operation	Ages	Time of Death, Months	Time Between Consultation and Operation
40	6	6 months	43	14	4 months
45	12	3 months	68	35	6 months
67	72	2 months	69	7	5 months
54	23	2 months	60	6	12 months
71	34	9 months	66	16	2 weeks
35	16	1 week	57	40	3 months
63	63	3 weeks	40	53	6 years
50	21	1 week	55	11	6 months
66	31	2 years	61	6	10 months

TABLE 4.—*Twelve Earliest Cases in Which Patients Died of Metastasis*

Time, Mos.	Age, Yrs.	Type of Operation	Interval Before Operation
3	40	Radical axillary dissection.....	4 years
4	76	Simple axillary dissection.....	20 years
4	58	Radical axillary dissection.....	2 years
4	45	Radical axillary dissection.....	10 days
4	45	Radical axillary dissection.....	7 months
6	36	Radical axillary dissection.....	5 months
6	48	Radical axillary dissection.....	3 months
6	59	Radical axillary dissection.....	2 years
6	36	Radical axillary dissection.....	36 years
7	36	Radical axillary dissection.....	4 months
8	48	Radical axillary dissection.....	4 months
8	30	Radical axillary dissection.....	6 months
Average 46.5			

occupied in the particular case prior to the emergence of the malignant growth.

Therefore, since these variables are determining factors in the production of the histologic pictures of carcinomas, and since one can neither control them nor assign to them their relative values in the general scheme, it should be obvious that the inherent vitality of the malignant growth is effectually distorted, if not entirely masked, and cannot be gaged. Small wonder that attempts at prediction are 50 per cent right and 50 per cent wrong!

TABLE 5.—*Twelve Earliest Cases in Which Patients Are Living and Well\**

Age, Yrs.	Metastasis †	Type of Operation	Interval Before Operation
44	No	Radical axillary dissection.....	2 months
54	No	Radical axillary dissection.....	3 weeks
78	Yes	Radical axillary dissection.....	4 weeks
56	No	Radical axillary dissection.....	4 years
55	No	Radical axillary dissection.....	2 years
61	No	Radical axillary dissection.....	6 months
44	Yes	Radical axillary dissection.....	4 months
46	No	Excision .....	5 weeks
48	No	Radical axillary dissection.....	6 months
51	No †	Excision .....	3 months
65	No	Excision axillary dissection.....	11 months
45	No	Excision axillary dissection.....	1 week
Average 54			

\* The smallest interval between the operation and the time of writing of these well patients was six years, four months; the longest interval was nine years.

† Two cases presented metastases and ten presented none.

TABLE 6.—*Age Distribution of the 100 Patients from Whom Specimens of Carcinoma of the Breast Came*

Age Group	No. Patients
28 to 30.....	4
31 to 35.....	4
36 to 40.....	11
41 to 45.....	23
46 to 50.....	19
51 to 55.....	15
56 to 60.....	9
61 to 65.....	6
66 to 70.....	6
71 to 75.....	1
76 to 80.....	2
Total .....	100

Further, in histologic grading one attempts, by examination of the removed specimen, to determine how it grew, and then to transfer this decision as a prediction of what will happen to any possible fragments left behind by the surgeon.

Is it not more accurate to determine by gross examination how a tumor grew? The patient says it was present for a certain length of time. How much did it grow in that time? Of course, one cannot know how long a tumor (in the breast) has existed. One can only hope to find out how long the patient has noticed it before she comes for consultation. But here sharp distinctions of time are not always

made. Most patients speak in round numbers, saying 6 months or 12 months rather than 5, 7, 11 or 13 months. This important fact is discussed and curves are given to illustrate it by Safford and me.<sup>11</sup> Naturally, one does not measure the rate of growth of a tumor, for, as a conscientious physician, one takes it out instantly.

If a malignant tumor is local for a certain length of time, however long or short, the operation should remove all the tumor and there is no need of grading it. But if a malignant tumor is general from the very beginning (as I think it is not) it is obvious that the variables are so complicated that one can see whether or not it recurs only by watching the patient, as has been done from the dawn of medicine.

TABLE 7—Operations

Outcome	Radical	Simple Amputation	Dissection of Axilla Simple Amputation	Removal of Tumor
Dead from metastases	72	1	7	2
Dead from other causes	14	5	1	0
Living, with recurrence	3	0	0	1
Living and well	9	0	3	4
Totals	78	4	11	7

TABLE 8—Axillary Involvement

Outcome	Positive, Clinically and Pathologically	Negative, Clinically and Pathologically	Clinically Positive, Pathologically Negative	Clinically Negative, Pathologically Positive
Living and well	0	4	3	5
Dead of carcinoma	31	11	3	14
Living, with recurrence	1	0	0	2
Dead of other causes	8	3	1	4

\* Axillary nodes were not removed in 10 cases.

The mass of evidence is, of course, in favor of the theory that tumors begin as local growths, without any general involvement. Unfortunately, the majority of patients are operated on when the growth is no longer local enough for complete removal.

The vital question is "Will the tumor come back?" It is clear that the answer does not lie in the microscopic but in the gross aspects. Did the surgeon leave any behind? If he did, the tumor will reappear from these fragments—unless they perish. And experience gives but little hope of this. If, on the other hand, the tumor is completely removed, there is no possibility of its return. It is all in a jar of

11 Reimann, S. P., and Safford, F. H. Statistical Study of the Influence of the Educational Campaign on the Interval Between Discovery and Consultation in Mammary Carcinoma, Rep. Internat. Conference on Cancer, London, 1928, p. 562

formaldehyde. In either case, attempts at grading the tumor are a waste of time. If in a patient from whom every vestige of the original growth was removed, another does develop, it must be a new one. Thereupon, I presume, one starts all over again and grades the new one. If some fragments have been left behind, one does not need to determine from the histologic preparation that the tumor will recur. It is known that it will. The only possible thing one can hope to grade is the rate at which the tumor will recur. The idea boils down simply to an attempt at guessing the rate of growth of unknown numbers and sizes of fragments in unknown positions left behind from a tumor which was partly removed surgically. And this cannot be done.

The question naturally arises, If fragments are left behind when a tumor is removed, why do they not immediately continue to grow instead of waiting for years as they often do (case 1)? Why do they grow at all? The answer to these questions is contained in the solution of the entire problem of cancer, which will not be had until a knowledge is obtained of the chemical basis of the regulation of cell proliferation. This has been intensively studied in this institute by Hammett, and in the succeeding paper he will put his results into a workable and investigatable hypothesis expressed in definite chemical terms.

#### SUMMARY

An attempt to grade the relative malignancy of 100 cases of cancer of the breast from the histologic picture of specimens obtained at operation gave false results, as determined by the later history of the patients from the follow-up records. A discussion of the biologic basis of this outcome, together with an inquiry into the rationale of the histologic grading of tumors, has been made. The conclusion is that the grading of a tumor for the individual patient is impossible at present.

# Laboratory Methods and Technical Notes

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## UNTREATED HUMAN BONE SECTIONED WITH NEW KNIFE \*

ARCH HIRAM MORRELL, M.D., NEW YORK

The delay in cutting sections of bone for microscopic study which is occasioned by the necessity for first decalcifying the bone is well known. It occurred to me that this might be obviated by using a knife of such hardness that it would cut sections of untreated bone. For this purpose a microtome knife was made from an alloy of tungsten carbide and cobalt which is manufactured under the trade name of "Widia." With this, sections varying from 6 to 12 microns in thickness have been cut from bone immediately after its removal during an operation and without any preliminary treatment. Other similar sections were cut from extremely dense undecalcified bone which had been fixed in a solution of formaldehyde.

In view of the fact that at present physicians have practically no knowledge of the chemical forms existing in living bone, whether colloid combinations or highly complex molecules of organic and inorganic substances, it is believed that the microscopic study and microchemical analysis of bone can now be approached in a manner heretofore impossible, with greatly increased possibilities of successful study.

420 East Fifty-Ninth Street.

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\* Submitted for publication, Oct. 22, 1929.

\* From the Pathological Laboratory, New York Orthopaedic Dispensary and Hospital.

# General Review

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## METHODS FOR THE HISTOLOGIC STUDY OF NORMAL AND DISEASED BONE \*

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NEW YORK

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Many methods have been developed for the study of bone because the various details of structure cannot be demonstrated by any single method. A survey of the methods may be found in Schaffer's<sup>1</sup> article in the Encyclopedia of Histological Technique and in Schmorl's,<sup>2</sup>

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\* Submitted for publication, Dec. 10, 1928.

\* From the Laboratory Division of the Hospital for Joint Diseases.

1. Schaffer, J., in Krause: Enzyklopaedie der mikroskopische Technik, Berlin and Wien., Urban and Schwarzenberg, 1926, vol. 2, p. 1148.

2. Schmorl: Die Pathologisch-Histologischen Untersuchungsmethoden, ed. 12, Leipsic, F. C. W. Vogel, 1922.



Mallory and Wright's<sup>3</sup> and Lee's<sup>4</sup> textbooks. In Schaffer's article, practically every method described to the year 1926 is covered. Many of the methods are critically surveyed and his personal observations, after about thirty years' work in the field, are given.

The approach to the problem of technic in the study of bone becomes easier when one considers that there are two main structural elements in bone—fibrils and cells. The fact that the fibrils are resistant to injury while the cells are easily injured or destroyed, and the fact that most of the methods for the demonstration of the fibrillar structure will not demonstrate the cells and their processes, show the necessity of approaching the study of bone with these facts in mind. Further, it is important, in selecting the methods for the study of bone, to differentiate between methods for an examination for diagnosis and those for a demonstration of structure.

The greater number of procedures for the study of bone deal with its preparation for normal histologic study. Formerly, such studies were made mostly on ground disks, the preparation of which the older histologists developed to a high degree of technical perfection. Sections are, of course, now used almost exclusively and, as I shall point out later, the sections demonstrate practically everything that ground disks do. To review the entire literature of methods for bone is unnecessary, but I shall discuss some of the more important problems in the preparation of bone for study and give some useful directions for staining.

#### DECALCIFICATION

In order to make sections of bone, it must be decalcified, and this is the foremost difficulty in preparing bone for study by staining. Nothing new has been added to the principles of decalcification for fifty years. No decalcifying fluid has been compounded that will decalcify hard bone without either injuring its nuclear structure or damaging its fibrils. Many weak organic and strong inorganic acids have been tried, with the result that, for the most part, only a few decalcifying fluids are used, though these are in many respects unsatisfactory. Animal bones seem to withstand decalcification better than human bones; this may be due to the difference in the compactness of the bone. In general, it may be said that mineral acids possess the greatest decalcifying power, but are most injurious to the nuclei, while the organic acids produce the greatest swelling of the fibrils but less injury of the nuclei, if the exposure to the acid is not too prolonged.

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3. Mallory and Wright: *Pathological Technique*, ed. 8, Philadelphia, W. B. Saunders Company, 1924.

4. Lee: *Vade-Mecum*, ed. 8, Philadelphia, P. Blakiston's Son & Company, 1924.

*Fixation of Bones That Are to Be Decalcified.*—As a rule, only well fixed material should be decalcified. Fixation in strong alcohol, mercuric chloride, saturated aqueous picric acid, Zenker's solution and Flemming's solution does not prevent the swelling of the collagenous fibers, but formaldehyde does prevent it. For studying adult bone, the most satisfactory fixative is a 10 per cent neutral aqueous solution of formaldehyde; even for embryonal bone, it is frequently necessary to use formaldehyde when certain staining methods are to be carried out.

The greatest number of the fixing solutions are weak acids or acid mixtures. They are therefore capable of acting on embryonal or poorly calcified bone as fixing and decalcifying solutions simultaneously. However, such solutions are useful only for small pieces of tissue. Zenker's or other acetic acid mixtures are of practical value for use with slightly calcified tissue.

*Decalcification After Embedding in Celloidin.*—Small, delicate tissues in which relationships must be preserved, as that in the internal ear, the cranium of small animals or zoologic objects, may be embedded in celloidin before decalcification. When the celloidin blocks are of proper consistency and air free, they are placed in water until they sink, and then they may be decalcified in aqueous acid mixtures, care being taken to secure quick decalcification by allowing free contact between block and acid. After the decalcification, the celloidin blocks are placed in 5 per cent lithium or sodium sulphate for twenty-four hours. They are then washed in running water for the same length of time. The blocks are transferred at length into alcohol, the strength of which is increased to 85 per cent. During this treatment, the celloidin does not lose any of its consistency or transparency.

*Decalcification of Dry, Macerated Bone.*—Dry, macerated bone should be placed in water or in a 0.5 per cent solution of sodium chloride for several hours before decalcification.

*General Directions for Preparation and Decalcification.*—Tissues to be decalcified should be cut into thin blocks, preferably under 2 mm. in thickness. This may be done with a fine jeweler's saw or, if the bone is soft, with a sharp knife or razor. If the latter is used bone dust does not enter between the trabeculae.

In addition to the right choice of a decalcifying fluid, it is of value in decalcification to use large amounts of the decalcifying agent, to agitate the fluid frequently, to decalcify at 37 C., to change the fluid frequently, to test the specimen and remove it as soon as decalcification is achieved and completely to remove all traces of the decalcifying agent before further treatment of the tissue. The progress of decalcification should be tested with a needle rather than with a nail or by bending the tissue.

Complete critical discussions of decalcifying mediums and conclusions are given by Busch,<sup>5</sup> Haug,<sup>6</sup> Schaffer,<sup>7</sup> Ziegler<sup>8</sup> and Lee.<sup>4</sup>

In the laboratory of the Hospital for Joint Diseases, New York, my associates and I have been constantly confronted with the problem of finding the proper decalcifying fluid to be used under given circumstances, for the fluid that should be used varies with the purpose of the examination and the character of the tissue to be examined. I shall describe in detail the use of the more important decalcifying fluids, and point out the pitfalls encountered in their use. The less important decalcifying fluids will be summarized.

*Decalcifying Agents in Use.*—Mueller's Fluid: This fluid is excellent for decalcifying fetal bones, if they are not too large. Mueller's solution has also been found useful for decalcifying spongy human bone (small pieces up to 2 cm. with thin cortex), bones of guinea-pig and rat, and pathologic human bone from osteomyelitis and tuberculosis. Large pieces of cortical bone or other compact bone could not be cut after the use of Mueller's solution. The sodium sulphate in Mueller's original solution is superfluous; a 2.5 to 5 per cent aqueous solution of potassium bichromate acts just as well. Decalcification may be hastened by using large amounts of the fluid, by keeping the tissues in an incubator at 37 C., by changing the decalcifying fluid at least twice a week and by stirring the solution daily. Mueller's is supposed to act as a fixative at the same time, but Haug denies that it does. It is advisable to fix bone tissues in formaldehyde before decalcifying them in Mueller's solution. After decalcification, the bones must be washed in running water for at least twenty-four hours.

The great disadvantage is that it takes weeks to decalcify spongy bone. During the long process of decalcification with Mueller's solution, there is a progressive hardening of the tissue, but I have found this action of the bichromate to be an advantage rather than a disadvantage when the bone was not too compact originally, for the bone is more easily cut after being embedded in paraffin. The nuclei of the cells may be injured if the tissue remains in Mueller's solution for too long a time, becoming pyknotic; but this is not a serious handicap, except when the finer nuclear structure of the bone cells is being studied. The distinction between dead and living bone remains, for in dead bone there is little, if any, nuclear staining. The fibrillar staining may be interfered with owing to the prolonged action of the potassium bichromate. The use of

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5. Busch: Arch. f. mikr. Anat. **14**:480, 1877.

6. Haug: Ztschr. f. wissenschaft. Mikr. **8**:1, 1891.

7. Schaffer, J.: Ztschr. f. wissenschaft. Mikr. **19**:359, 1902.

8. Ziegler, P.: Festschr. zum siebenzigsten Geburtstag von Carl v. Kupffer, Jena, 1899.

Mueller's solution for decalcifying was developed by Pommer, who found it particularly useful for differentiating osteoid tissue from real bone.

The slow action of Mueller's fluid may be improved by combining it with nitric acid 0.5 to 1 per cent. Schmorl<sup>2</sup> recommended 3 per cent nitric acid. However, unless the bone is compact, nitric acid should not be resorted to. For giving a generally stained picture of bone for diagnostic purposes it has proved to be the best decalcifying fluid in my experience.

**Nitric Acid:** Nitric acid is effective for large pieces of bone and it is conceded to be the best decalcifying agent among the strong acids. It cannot be used for the study of fibrils examined by the polarizing microscope. It causes little swelling of the tissue when used in a 5 per cent solution. In other solutions, the degree of swelling of the tissue that it will cause depends on the concentration of the acid. Busch observed that prolonged treatment in a dilute acid was more injurious to the tissue than a short stay in a strong acid. Nitric acid has been used in watery solution in strengths of from 1 to 10 per cent. Many have recommended its use with substances that prevent swelling, such as chromic acid, mercuric chloride and phloroglucin. Schaffer is of the opinion that the addition of such substances to the watery solution of nitric acid is not only unnecessary but to a great degree injurious to the tissues. Recently, Küster, Schmorl, Preiswerk and others have also discarded the use of such substances. There is experimental proof that a solution of 5 per cent nitric acid made up in 95 per cent alcohol is only one-fifth as effective as the 5 per cent aqueous solution. Furthermore, nitric acid dissolved in diluted alcohol shrinks and thickens the collagenous fibers.

As for decalcification with nitric acid, it needs only the 5 per cent watery nitric acid followed by the essential treatment in 5 per cent lithium or sodium sulphate for twenty-four hours, during which the fluid is changed until it gives a neutral reaction with litmus, and washing for from twenty-four to forty-eight hours in running water. The use of much stronger solutions hastens decalcification only slightly and may injure the tissues severely. The tissues should be well fixed and should be placed in the acid immediately after the fixative has been washed out by water. Agitation of the tissue while in the decalcifying fluid reduces the time necessary for its decalcification. Decalcification is much hastened if the container is placed in a mechanical shaking machine. If the tissue is not agitated, its surface becomes coated with bubbles of gas which impede the action of the acid. If the pieces are large or compact, the acid should be changed several times, particularly in the beginning.

Some maintain that human bones may remain in nitric acid for four days without suffering serious injury. However, the tissues must remain in the acid only as long as is necessary for their complete decalcification; for, in my own experience, the stainability of the nuclei is greatly impaired if the tissues remain in the acid for one day. While nitric acid is recommended, when a strong acid must be used for tissues to be subsequently stained, nevertheless, I cannot endorse it as wholeheartedly as Schaffer and Mallory do for human bones.

If the nitric acid destroys the nuclei, it is then often impossible to differentiate between living and dead bone.

**Hydrochloric Acid:** Hydrochloric acid quickly and effectively decalcifies large pieces of bone, but it destroys the nuclei. Therefore, it can be recommended only for the demonstration of fibrillar structures of bone; for this it is unexcelled. In dilute solutions, hydrochloric acid causes more swelling than in concentrated solutions and, to prevent swelling of the tissues, it, too, has been used in combination with many substances such as chromic acid, phloroglucin and alcohol.

The method originated by von Ebner<sup>9</sup> in 1874 gives excellent results in the preservation of the fibrils and lamellar structures. Romeis<sup>10</sup> and Petersen<sup>11</sup> recently corroborated the value of this fluid for such studies. Large amounts of the fluid should be used, and it should be changed frequently. Petersen used concentrated hydrochloric acid made up as a 5 per cent solution in 10 per cent sodium chloride. After decalcification, the bone is placed in a 10 per cent solution of sodium chloride, to which small amounts of an alkali, such as lithium carbonate, are added until the solution is neutral. The tissue remains in the neutralized solution of sodium chloride for forty-eight hours, after which the bone is washed in running water for twenty-four hours and dehydrated in the usual way. Before decalcification, good fixation is necessary and fixation in a 10 per cent neutral solution of solution of formaldehyde or 95 per cent alcohol is the most desirable. This is the method used when the fibrillar structure is to be studied by polarized light.

*Less Important Decalcifying Fluids.*—**Formic Acid:** This produces the greatest swelling of the collagenous tissues, and may be used for decalcification of bone only after the bone has been fixed in formaldehyde. The addition of chromic acid or gold chloride moderates the swelling. Schaffer, using formic acid, specific gravity 1.2, was able to decalcify a section of human tooth from 1 to 1.5 mm. thick in twenty-four hours. The tissue should be transferred directly into strong alcohol after decalcification.

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9. Von Ebner: Sitzungsab. d. k. Akad. d. Wissensch. **71-72**:49, 1875.

10. Romeis: Naturwissenschaften **10**:733, 1922.

11. Petersen: Methoden zum Studium der Knochens, Ztschr. f. wissenschaftl. Mikr. **43**:355, 1926.

**Chromic Acid and Chromic Acid Mixtures:** Pure chromic acid has a slight decalcifying action. It is used best in a 1 per cent solution for tissue containing little calcium. Its greatest usefulness is in being added to other acids to prevent swelling, as for instance when it is used as 0.5 per cent chromic acid in 1 to 2 per cent nitric acid.<sup>12</sup> For delicate objects, the following is recommended: 1 per cent osmic acid 10 cc., 1 per cent chromic acid 25 cc. and water 65 cc. After decalcification, the tissues are placed in 70 per cent alcohol in the dark.

**Acetic Acid:** According to Schaffer,<sup>7</sup> acetic acid causes much swelling of the tissues when used alone. A mixture of equal parts of saturated aqueous solution of sodium chloride (about 30 per cent) and concentrated acetic acid (50 per cent) decalcifies slowly but prevents swelling and shrinking. If the acetic acid is combined with osmic acid or gold chloride, or if the tissues have first been fixed in formaldehyde, the swelling is also lessened. In combination with bichromate, it is used as Zenker's fluid by some for decalcification of small pieces of bone.

**Lactic Acid:** Though Haug<sup>6</sup> and Ziegler<sup>8</sup> reported lactic acid satisfactory when used in 10 per cent solution, Busch and Schaffer found that it caused marked swelling of the tissues.

**Phosphoric Acid:** Phosphoric acid was also used in 10 and 15 per cent solutions and found, on the whole, unsatisfactory.

**Citric Acid:** Citric acid acts like phosphoric acid, but injures the cells.

**Picric Acid:** In saturated watery solutions, picric acid is good for use in the preparation of small fragments of bone, and has been used in combination with 3 to 5 per cent nitric acid for larger bones.

**Sulphuric Acid:** In 5 per cent aqueous solution, sulphuric acid is a good decalcifying agent for large pieces of bone, but it causes swelling of the tissues. The swelling recedes after the washing. It does not offer any advantage over nitric acid and it causes precipitates to form in the tissues, which, however, may be washed out with water.

**Trichloroacetic Acid:** In 5 per cent aqueous solution, trichloroacetic acid acts quickly, causes much swelling and necessitates treating the bone with alcohol directly after the decalcification. It does not have any special advantages.

**Sodium Citrate:** Recently, a 20 per cent solution of sodium citrate in a 10 per cent solution of solution of formaldehyde was recommended as a rapid and satisfactory decalcifying agent. I found that with bones of normal rats it acted more slowly than Mueller's fluid.<sup>13</sup>

12. Ranvier: *Traité technique d'histologie*, Paris, F. Savy, 1889. Gebhardt: *Arch. f. Entwcklungsmechn. d. Organ.* **10**:137, 1900.

13. Shelling, D. H., and Halperson, May B.: *A Rapid Method for Decalcification*, *Arch. Path.* **5**:835 (May) 1928.

## THE PREPARATION OF DISKS AND SECTIONS

*General Procedure.*—Bone may be prepared for histologic examination by being decalcified or it may be studied without decalcification. In the latter case, ground disks are made of fresh (fixed or unfixed) or macerated bone, or tiny fragments are scraped from the bone with a scalpel and studied. The disks or fragments may be examined unstained with the polarizing microscope, or stained or unstained with the ordinary microscope. The decalcified bone may be cut with a freezing microtome or may be embedded either in celloidin or in paraffin. Paraffin and celloidin sections are stained, and frozen sections are examined either stained or unstained. This is the general procedure for decalcified bone.

As to the superiority of the celloidin over the paraffin preparations in the study of bone there is doubt. I have used both and prefer paraffin preparations for all but extremely large sections. If Florida cedar wood oil is used for clearing the tissues instead of xylene, which makes the tissues brittle, and if the tissues are not permitted to remain for more than three hours in the paraffin oven, good sections will be obtained, provided a sharp knife is used. After decalcification, bone may be handled in the same way as any other tissue, except that care must be taken lest stained sections of bone that have been cleared with xylene, which renders them brittle, do not fall off the side.

*The Preparation of Undecalcified Bone.*—Fragments and Hand Cut Sections: Tiny fragments of normal or pathologic bone from which the soft tissues have been scraped with a scalpel may be examined directly under the microscope by placing them in a solution of sodium chloride. Glycerin should not be used.

The spongy bone of younger animals, as, for instance, the condyles of the femur of the young rabbit, may be easily cut with a sharp knife, and preparations may be obtained which may be examined directly under the higher power magnifications with or without staining.

*Ground Disks:* For the preparation of large cross sections or longitudinal sections of bone without decalcification, the grinding methods must be used. There are many methods of preparation, the disks being prepared with files, grindstones or grinding powders. On the whole, the powders are considered unsatisfactory. The choice between grindstones, files and powders is one of individual preference. The file method, while possibly a little more difficult, is conceded to give the best disks.

If disks are to be prepared from dry bones without soft parts, the bones must be carefully macerated and completely defatted. Disks may also be prepared from fixed or from fresh bone. Exact directions for the maceration of the bone are given by Ranvier.<sup>12</sup> The bone, which

should be fairly fresh, is separated from all its soft parts, the marrow cavity is opened, but the bone is not permitted to dry. The bones are then placed in water and kept in a warm place for several weeks or months. They are then brushed under a forceful stream of water and placed in the air to dry, but not in the direct sunlight. They must become completely white. If they show yellowish transparent areas, it indicates that they still contain fat and they must be defatted by treatment with benzene, toluene or xylene at 37 C. The disks may now be ground.

Gebhardt,<sup>12</sup> who is acknowledged to be highly competent with the disk method, gave the following directions: After the bone is macerated, it is placed in a vise and cut with a fine hand saw, the section being thick enough so that it does not bend. One surface of the section is ground with a file until it is even and the filings are removed with a stiff brush. The bone is then smoothed and polished by rubbing on frosted glass. Some thick, warm Canada balsam is placed on a glass slide, and the piece of bone with the ground surface downward is pressed with the fingers against the slide until the balsam hardens, care being taken that the balsam does not become brittle. Then the other surface of the bone is ground with files of increasing fineness until the finishing point is reached, at which the disk is transparent. Gebhardt frequently obtained sections that were less than 30 microns in thickness. The filings are removed by a stiff brush. Then this side of the bone is polished on a plate of frosted glass. The surface is then covered with warm balsam and mounted under a coverslip. Gebhardt usually prepared small disks, rarely over 2 or 3 cm. in the largest dimension.

For fine objects that might be injured in the grinding or polishing, or when preparations of bone and its soft parts are wanted, the bone should be embedded entirely in Canada balsam. Sections are then cut with the saw and ground. In Reinicke's<sup>14</sup> method, thick Canada balsam is warmed in an iron vessel, and the tissue is placed in it. Together they are warmed carefully and slowly. If the heating is too fast, the Canada balsam becomes brittle and the preparation will be unsatisfactory. The balsam is tested from time to time with a needle; if the balsam remaining on the needle hardens quickly and does not become indented by the finger-nail, then it is thick enough. The bone is removed, the balsam is permitted to dry and the bone is cut into sections with a saw. One surface is smoothed and the disk is glued with balsam to a clean, warm slide and ground. Care must be taken that air bubbles do not exist between the block and the tissue. The grinding and polishing are done as described.

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14. Reinicke: Beitr. z. neueren Mikr., 1860, vol. 2, p. 57.



The preparation of moist disks of fresh bone or bone fixed in alcohol was first recommended by Volkmann<sup>15</sup> and also used by Matschinsky<sup>16</sup> and Gebhardt.<sup>12</sup> These disks are prepared in the same way as those of macerated bone. The advantage of using fresh or fixed bone is that the bone may be stained after the disks are prepared. Volkmann preferred making disks of fixed or fresh bone because he felt that he could demonstrate certain pathologic changes of the bone ground substance, as for instance granular cloudiness, molecular disintegration and the appearance of calcium granules, which, according to him, are shown only by this method.

*Preparation of Decalcified Bone.*—Decalcified bone may be embedded in celloidin or paraffin and studied in stained sections, as stated. It may also be cut on the freezing microtome, and the frozen sections may be examined either stained or unstained. Unstained frozen sections are, in practically every way, as good or better than ground disks, and they may be substituted for ground disks, except when the calcium of the ground substance is the object of the investigation. Petersen recently emphasized the usefulness of this procedure. My own experience justifies considerable enthusiasm. I have examined frozen sections under the polarizing microscope and have obtained pictures in every way as good as those presented in Gebhardt's article. I have seen disks that were distinctly inferior to frozen sections, although they were prepared at much greater effort. The simplicity of the preparation of frozen sections in itself is a distinct advantage. The best frozen sections are obtained from cortical bone, sections of spongy bone sometimes falling apart.

To secure good frozen sections of spongy bone, the trabeculae must be supported by some solid medium. Pieces of spongy bone are infiltrated with a 12.5 per cent aqueous solution of gelatin for four hours or longer in the incubator at 37 C. and then for an equal period in a 25 per cent solution. The entire container is then removed from the incubator. The gelatin is allowed to harden, and is then covered with 10 per cent solution of solution of formaldehyde. Before being frozen, the block must be trimmed and washed in running water for about an hour. Gelatin blocks must be over-frozen and then allowed to warm up a bit before cutting, as the inside is hard to freeze. Good sections are obtainable. I do not know of any way to remove the gelatin without spoiling the section. However, the gelatin does not interfere with examination of the sections under polarized light or of the stained sections.

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15. Volkmann: Arch. f. klin. Chir. 4:437, 1863.

16. Matschinsky: Arch. f. mikr. Anat. 39:151, 1892.

THE FURTHER TREATMENT OF DISKS AND SECTIONS  
OF BONE

When disks or sections of bone are prepared, one is ready to study the structure of bone. One can study (1) the ground substance, which includes the fibrils, cement lines, Sharpey's fibers, elastic fibers and the inorganic salts; (2) cellular elements, which include the osteoblasts and the bone cells with their processes; (3) the architecture of the bone; (4) the growth or epiphyseal regions; (5) the zones of preparatory ossification of normal bone and the so-called osteoid tissue of pathologic bone.

*Demonstration of Structures in the Ground Substance of Bone.*—The fibrils of bone may be shown in ground disks, frozen sections or stained sections. The first and still classic studies on the fibrillar structure of bone were done by von Ebner in 1874.<sup>9</sup> Gebhardt,<sup>17</sup> in studying the fibrillar structure of bone, used only disks, prepared, for the most part, from fresh bone by the method described. He pointed out that von Ebner's fluid, if the bone is to be decalcified, is the best solution to use, for it avoids injury of the fibrils and permits examination of the bone with the polarizing microscope. Bone that has been treated with phenol or phenol derivatives cannot be used for polarizing work, because the phenol changes the refractive index of the collagenous fibers. For the study of fibrils, Gebhardt mounted his disks in balsam and examined them with the polarizing microscope.

Weidenreich<sup>18</sup> studied the fibrillar and lamellar structure of bone using a modification of the Matschinsky silver method on disks of macerated bone. The disks prepared from macerated bone are washed in distilled water, and then placed in a 1 per cent solution of silver nitrate, in which they remain for twenty-four hours in the dark. After being washed with distilled water, they are placed in 10 per cent solution of solution of formaldehyde for one hour at 50 C. The disks stain dark brown. After the washing in water, it is necessary to grind the bases of the disk on a file or slate stone until the surface precipitate is removed. The disks are washed in water and then placed for about six hours in a 5 per cent solution of sodium thiosulphate and then for twelve hours in running water. Then they are dehydrated in alcohol, and embedded in Canada balsam. I impregnated the piece of bone first, then attached it to a slide and ground it down with a file and embedded the disk in balsam. To demonstrate the fibrillar structure better, instead of placing the disks for one hour in 10 per cent solution of solution of formaldehyde at 50 C., Weidenreich placed the disks in the same solu-

17. Gebhardt: Arch. f. Entwcklungsmechn. d. Organ. **20**:199, 1905-1906.

18. Weidenreich: Knochenstudien: 1. Teil, Ztschr. f. d. ges. Anat., abstr. 1, Ztschr. f. Anat. u. Entwicklungsgesch. **69**:382, 1923.

tion for twenty-four hours at room temperature and then treated the disks in exactly the same way.

Weidenreich said that many times he got excellent results by these methods but that the results were not uniform. He then made use of the Weigert fibrin method, which he found satisfactory.

Weidenreich<sup>18</sup> modified Weigert's fibrin method in regard to differentiation and used this method successfully to demonstrate the fibrillar structure of bone and the cement lines. Five per cent nitric acid was used for decalcification and the tissues were embedded in paraffin. The method used is the same as that given in Mallory and Wright's<sup>3</sup> book on pathologic technic, eighth edition, page 191 up to step 7, or in Schmorl's<sup>2</sup> book, editions 12 and 13, to step 5, on page 146. The only modification is in the differentiation, which he carried out as follows: After the sections have been washed in water and blotted, they are differentiated in a mixture of three parts xylene to one part aniline oil, then two parts xylene to one part aniline oil, then one part xylene to one part aniline oil. The aniline oil must be of a high grade. As differentiation progresses, stain is extracted more slowly, and it is necessary to leave the sections in the differentiating fluid longer. Continued control with the microscope is necessary. Differentiation must be carried on until a stain is not given off, and fibers appear sharply in the ground substance, which is almost completely decolorized. The sections must then be well cleared in xylene and mounted in balsam. If the nuclei are to be stained, it must be done before the fibrils are stained. After trying various carmine solutions, I found that staining with lithium carmine for about five minutes and differentiating with acid alcohol gives a clear red nuclear stain, which stands out nicely in contrast to the blue fibril stain. I have used this method on embryonal and adult lamellar bone. The results, despite every care in differentiation, are not uniformly good. Coarse-fibered embryonal bone gives better results than adult lamellar bone.

This method is supposed not to be applicable after fixation or mordanting of tissue in fluids containing chrome salts. The best fixative is supposed to be alcohol. After the treatment with chrome salts, the sections should be treated before staining for from one-half to one hour with a 0.33 per cent solution of potassium permanganate, then washed in water and treated with 5 per cent oxalic acid for from two to three hours. After being thoroughly washed, they may be stained. After Zenker fixation, such preliminary treatment has been found unnecessary. Excellent results have been obtained using Weigert's original method with or without the modification, by controlling the degree of differentiation under the microscope.

Studnicka<sup>19</sup> used Bielschowsky's method for bone fibrils, fixing the bone in formaldehyde and decalcifying it in nitric acid. Directions for the subsequent treatment may be found in any standard textbook. Using this method, I have obtained some strikingly beautiful preparations, especially of the cement lines and general architecture of cortical bone. However, the results were not by any means uniform. The chances of success are greatest when thin frozen sections are used.

The fibrils were studied by Petersen<sup>11</sup> in frozen sections of bone examined with the polarizing microscope. I have found this to be the simplest method of demonstrating fibrils. The bone is fixed in formaldehyde solution and decalcified in von Ebner's fluid as described under the head of decalcification. Then pieces are cut on the freezing microtome, the sections being from 40 to 50 microns in thickness. Thicker sections give better pictures of the perforating canals and the architecture of the substantia spongiosa. These sections are studied unstained. Unstained preparations for the polarizing microscope give the best pictures by Petersen's method when mounted in watery solutions. They are mounted in a medium such as 5 per cent chloral hydrate, 10 per cent sodium chloride with 5 per cent chloral hydrate, or a mixture of 10 per cent sodium chloride and 10 per cent calcium chloride with 5 per cent chloral hydrate. The sections must be fat-free. If fat is present, rapid transference from water through alcohol to xylene and through alcohol back into water removes it completely. Wrinkles must not be considered, because in water the tissue becomes smooth. Remnants of periosteum must be carefully removed with a soft brush and all smudges cleaned away from the glassware, for these things interfere with the examination under the polarizing microscope. Air bubbles must be carefully avoided, for they attach themselves to the section. Finally, the cover glasses must be sealed with wax colophonium cement, more wax than colophonium, so that it is viscid and not brittle. The wax colophonium cement is prepared as follows: 500 Gm. of colophonium is melted over a low flame, and 125 Gm. of yellow bee's wax, 200 Gm. of yellow ochre and from 3 to 5 Gm. of linseed oil are added, the mixture being all the while stirred well. The mixture is just allowed to come to a boil and is then removed from the flame. It may be poured into paper molds of convenient size and allowed to harden. Before use for sealing, it is melted slowly. Large slides and cover glasses that extend beyond the section are indispensable. The preparations last long, but it is necessary that the cement be in good condition.

To demonstrate the bone fibrils under the polarizing microscope, the sections may be treated with phosphotungstic acid, which does not greatly change the double refraction. The sections may be enclosed

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19. Studnicka: *Ztschr. f. wissenschaft. Mikr.* **23**:414, 1906.

directly in 5 per cent phosphotungstic acid, or may be left in this solution for from twelve to twenty-four hours and then enclosed in a solution of chloral hydrate. I have found that this treatment is not essential.

**Sharpey's Fibers:** Formerly, Sharpey's fibers were demonstrated by isolation or in disks, but more recently they have been demonstrated in sections. It is important to use the proper material, for while Sharpey's fibers may be demonstrated rather consistently in the fiber bone of the primary fetal skeleton they are rarely seen in adult cortical bone, and then only in the ground lamellae. There are numerous methods given in Schmorl's textbook and in Schaffer's review, including chemical processes, and staining and impregnation methods. Most of them are not consistently successful, and it seems that with the proper material Weidenreich's modification of Weigert's fibrin stain is the best.

**Elastic Fibers:** The methods for staining sections of bone for the study of elastic fibers are the same as for staining soft tissue, and again Weigert's fibrin stain can be recommended. Von Ebner advises the use of fresh tissue only, if disks are used; in macerated bone the elastic fibers may be dissolved. Chemical methods are employed, such as boiling a piece of bone for a short time in sodium hydroxide or boiling for a day in water. Koelliker boiled sections in acetic, oxalic or hydrochloric acid or else he removed the elastic fibers with cold potassium or sodium hydroxide. Elastic fibers are demonstrated best in the periosteum.

**Cement Lines:** To demonstrate the cement lines, frozen sections of bone decalcified according to von Ebner's method may be stained with Bielschowsky's silver stain. These structures are shown best in cortical bone.

**Calcium:** The calcium of the ground substance may be demonstrated in disks or sections either by staining methods or by chemical methods. For the microscopic demonstration of calcium in the ossifying skeleton, Schuscik<sup>20</sup> used embryonal bone fixed in alcohol, if the bones were to be embedded in celloidin, and in 10 per cent solution of solution of formaldehyde for fifteen minutes, if frozen sections were to be cut. She reported that all other fixatives and even water decalcify bone.

The surest way of demonstrating that a tissue contains calcium without locating it in the section is through the formation of crystals of plaster of Paris. Undecalcified sections are (1) placed in 40 per cent alcohol, (2) then on a slide, and (3) a drop of 2.5 to 3 per cent sulphuric acid is placed on the edge of the section: crystals of plaster of Paris appear quickly.

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20. Schuscik: *Ztschr. f. wissenschaft. Mikr.* **37**:215, 1920.

In none of the methods of staining for calcium, with the exception of the method of von Kóssa, in which silver nitrate is used, is there exclusion of the staining of the organic ground substance. Since all such methods stain calcium-free Müller preparations positively, only von Kóssa's method can be used without confusion.

The silver method of von Kóssa is as follows: (1) The bone is fixed in alcohol or for a very short time in formaldehyde, and then, is washed in alcohol; (2) frozen, paraffin or celloidin sections (as preferred) are cut; (3) the sections are stained for from thirty to sixty minutes, in sunlight, in a 1 to 5 per cent solution of silver nitrate; (4) then they are washed in distilled water; (5) the excess silver salt is removed by placing the section in 5 per cent sodium hyposulphate; (6) the sections are washed in distilled water, and (7) counterstained with safranin, dehydrated and mounted in balsam.

The sections show yellowish staining of the calcified areas, which soon become black. Von Kóssa's method stains both calcium carbonate and calcium phosphate and is not selective for the latter. Even when this method is negative for calcium, the plaster of Paris method with sulphuric acid may be positive. Stains for staining calcium phosphate selectively have not been found.

*The Cellular Structure of Bone.*—The two kinds of cells with which one is concerned in the study of bone are the osteoblasts and the bone cells. To demonstrate the osteoblasts or the bone cells without their processes in a gross way is a simple matter. In any fixed preparation, they may be stained with the usual dyes, provided that the decalcifying agent, if one has been used, has not destroyed them. All the strong inorganic acids are destructive of the cells and their nuclei but nitric acid is, perhaps, of them all, the least destructive. This must be kept in mind particularly when diagnosis is concerned, for on the stainability of the nucleus depends the decision as to whether the bone is living or dead. If one is interested in studying the cells of the bone, a strong acid should not be used. But decalcification for a long time in Mueller's solution also injures the cells, so that it is evident that any minute cytologic studies on bone must be done on bone that is quickly decalcified or that does not need decalcification.

**Bone Cells:** One of the oldest and simplest methods of study of bone cells uses fresh, thin bone plates that have been deprived of periosteum. These are stained in carmine and mounted in glycerin. The nuclei and the protoplasm of the bone cells stain but not the processes. Satisfactory pictures of bone cells are obtained when thin pieces of young embryonal bone are fixed in Zenker's solution and sections of the undecalcified bone are stained with Delafield's hematoxylin and congo red or eosin. In such preparations, a few short protoplasmic processes may be demonstrated. Beautiful pictures are obtained when embryonal

or young infant bone is decalcified in Mueller's solution and stained by Mallory's eosin and methylene blue (methylthionine chloride, U. S. P.) method.

**Bone Cell Processes:** The problem becomes more difficult when, in addition to the cells, the processes are to be demonstrated. Bast<sup>21</sup> fixed extremely thin plates of periosteum-covered mammalian bone in 95 per cent alcohol, placed them in water and stained them from eight to twenty-four hours in a very weak aqueous solution of gentian violet. He dehydrated them as quickly as possible, placed the bone plates in benzene or xylene and then removed the periosteum completely. He mounted the bone plates in warm, thick, neutral balsam. With this method, the bone cells and their processes appear deeply stained; the older the bone, the clearer the staining. They are best seen under oil immersion. To prevent the stain from coming out, the absolute alcohol should be removed completely by several changes of benzene. I have found that Bast's method clearly demonstrates bone cells and their processes, but it is useful only when extremely thin plates of bone are obtainable; for example, the skull and nasal bones of young or embryonal animals. I was unable to use this method on the long bones of either young or embryonal animals because thin sections covered with periosteum were not obtainable.

Zachariades<sup>22</sup> demonstrated the processes of bone cells in the canaliculi in sections of freshly fixed fetal bone decalcified with acid and cut by hand or on the freezing microtome. According to his directions, a section is placed on a slide and treated for a few seconds with 1 per cent osmic acid for the fixation of the protoplasmic net. It is then washed and stained quickly in one drop of watery saturated solution of safranin. Then the section is covered with a few drops of 40 per cent potassium hydroxide and is slightly warmed until it becomes flat. The excess of potassium hydroxide is removed, and the section is covered with glycerin water. If the treatment with potassium hydroxide has not been too severe, the lacunae and the canaliculi of the bone may be seen, and, in addition, protoplasmic processes may be seen entering the canaliculi. Few processes are seen as compared with the number of canaliculi.

The best way to demonstrate the protoplasmic processes of the bone cells is as follows.<sup>23</sup> A well polished disk of fresh bone is made. The disk is stained for twenty-four hours in aqueous quinolin blue solution (a few drops of the alcoholic solution in 10 cc. of distilled water). The precipitate is removed with a brush before mounting. The protoplasmic processes are seen in the canaliculi, and they stain red. These

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21. Bast: *Am. J. Anat.* **19**:139 and 321, 1921.

22. Zachariades: *Ztschr. f. wissenschaft. Mikr.* **10**:447, 1893.

23. Zachariades: *Compt. rend. Soc. de biol.* **1**:207, 1889.

processes are so delicate in lamellar bone that there may be some difficulty in seeing them. In fiber bone, they are easily demonstrable.

The demonstration of the bone cells and their processes in paraffin or celloidin sections by the gold impregnation and chrome silver method of Golgi <sup>24</sup> has been suggested, but these methods are, on the whole, not reliable, as pointed out by Schmorl.

Lacunae and Canaliculi: While the bone cells and their processes are difficult to demonstrate, the lacunae and the canaliculi in which they are enclosed in the ground substance are easily demonstrable. The walls of the lacunae are seen in ordinary sections stained with hematoxylin and eosin. The lacunae and the anastomosing canaliculi have always been demonstrated in unstained dried disks mounted in balsam or unmounted. I have been demonstrating the lacunae and canaliculi in frozen sections of acid decalcified bone by thoroughly drying the frozen sections, which should be rather thick, on smooth filter paper and mounting rapidly in glycerin or balsam. I prefer the glycerin. The lacunae and the thick network of anastomosing canaliculi stand out black and distinct on a transparent colorless background. While the results are as good as any of the results obtained by any method pictured in the literature, they are only temporary, rarely lasting for more than four or five days. The reason for this is that the method depends on the presence of air in the lacunae and canaliculi, but after a few days the air that was present in the dried section is replaced by the mounting medium, whether it is balsam or glycerin. I have not seen this method mentioned anywhere in the literature. It is simple and effective.

Finer Cytologic Details: In addition, several other details have been studied particularly in the osteoblasts of embryonal bone. These are the mitochondria, the Golgi apparatus, the secretion spheres of the protoplasm and the basophilic nature of the protoplasm.

For the demonstration of mitochondria in osteoblasts, Dubreuil <sup>25</sup> fixed thin plates of perichondral and endochondral embryonal bone from near the epiphysis in a mixture of bichromate and formaldehyde solution for from two to three days, then for eight days in 3 per cent potassium bichromate. After being washed, the bone was embedded in celloidin, decalcified in 5 per cent nitric acid, as described under decalcification, and stained with Heidenhain's iron hematoxylin. Deineka <sup>26</sup> also gave a good method.

For the demonstration of the secretion spheres in the protoplasm of osteoblasts as described by Dubreuil, embryonal bone is fixed in Lenhos-

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24. Joseph: *Arch. f. mikr. Anat.* **6**:182, 1870. Bouin: *Bibliog. Anat.* **4**:207, 1896.

25. Dubreuil: *Ann. d'anat. micro.* **15**:53, 1913.

26. Deineka: *Anat. Anz.* **46**:97, 1914.



sék's mercuric chloride acetic acid mixture<sup>27</sup> for from six to twelve hours, then in 3 per cent potassium bichromate for a few days, and paraffin or celloidin sections are stained in iron hematoxylin.

For the demonstration of basophilic protoplasm of the osteoblasts, M. Askanazy<sup>28</sup> recommended staining sections of embryonal bone in concentrated watery solutions of Loeffler's methylene blue, or Unna's polychrome methylene blue. Differentiate in alcohol or aniline alcohol (1:10). If the bone also is to be stained, the following procedure is recommended: (1) stain the bone for from five to ten minutes in methylene blue, (2) wash it in water and (3) place it for from two to five minutes in 95 per cent alcohol plus two parts of saturated alcoholic eosin solution.

*The General Architecture of Bone.*—In studying the general structures of lamellar bone, a piece of dense cortex of a tubular bone should be examined. Any of the methods given for fibrils serves also for this purpose. Frozen sections of bone decalcified by von Ebner's method, and mounted in 5 per cent chloral hydrate, examined with an ordinary microscope, yield most satisfactory pictures when the light is cut down. Frozen sections that have been blotted dry may be examined under a coverslip without a mounting medium. A good stain for the general architecture of the bone is gallein, as described by Petersen. One tenth of a gram of powdered gallein is added to 100 cc. of boiling 5 per cent aluminum chloride and boiled for fifteen minutes. It is made up to volume and filtered, and paraffin, celloidin or frozen sections are stained for from twelve to twenty-four hours or more in a solution of one part stain to ten parts water. In my own experience with the stain, the dilute solution of gallein prescribed by him gave poor results, but with a half strength solution informative pictures were obtained after staining for from twenty-four to forty-eight hours. This may be due to the difference between European and American gallein. After being stained, the sections are washed in water to remove the excess stain and covered with 95 per cent alcohol, the excess being allowed to run off on filter paper. They are either preserved in 96 per cent alcohol or further dehydrated in absolute alcohol and cleared in xylene and mounted in balsam. Before being cleared and mounted, the sections may be treated with a 5 per cent solution of phosphotungstic acid for twenty-four hours, which makes the fibrils stand out especially well.

*The Epiphyseal Region of Bone.*—Endochondral Ossification: To demonstrate endochondral ossification, bone and cartilage must be dif-

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27. Lenhossék's fixative is made up as follows: saturated aqueous solution of sublimate, 75 cc.; glacial acetic acid, 5 cc., and 50 per cent alcohol, 25 cc., with saturation of the mixture with picric acid.

28. Askanazy: Zentralbl. f. path. Anat. **13**:369, 1902.

ferentiated. Generally, I use a double stain that is basic for the cartilage and acid for the bone. The staining of cartilage depends on the treatment it has had. Mueller's fluid dissolves and extracts the chondroitin-sulphuric acid and the cartilage does not give the characteristic stain with the basic dyes, but with Mueller's fluid it is possible to differentiate sharply the calcified from the uncalcified cartilage.

According to Schaffer,<sup>1</sup> page 1191, Escher fixes his material in picric mercuric chloride, decalcifies in alcoholic hydrochloric acid, treats sections with concentrated Delafield's hematoxylin for three minutes and then with alcoholic borax carmine for twenty-four hours. He then puts the sections in alcoholic orange G for a short time, clears them in carbolxylene and mounts them directly in balsam. The bone appears red, the cartilage blue.

In studying embryonal bone, I stained tissue decalcified by Mueller's method with Mallory's eosin and methylene blue method; with this procedure the bone and osteoid tissue stain red and the cartilage matrix stains blue, the intensity varying directly with the amount of calcium in the ground substance.

*Preparatory Ossification Zones and Osteoid Tissue.*—To demonstrate previously calcified areas in decalcified bone, Pommer recommended using Mueller's fluid in the case of embryonal bones after the first half of embryonal life. In such bones, not completely decalcified with Mueller's fluid, a clear difference is seen between the pale red osteoid substance and the intense red finished bone, when Delafield's hematoxylin and eosin are used.

The aniline dyes used by Pommer are more differential. His method is based on the belief that Mueller's solution does not entirely remove the calcium from the bone; it carries decalcification on to the stage in which bone can be cut. Pommer emphasized that decalcification with Mueller's fluid should be stopped when the tissue may be cut with a razor with the resistance of hard wood. Because Mueller's fluid does not decalcify completely, the bone containing calcium is supposed to be distinguishable from the bone that does not contain calcium (osteoid tissue) by special staining methods. When dilute ammonia carmine is used (see Schmorl<sup>2</sup> 12th and 13th editions, pages 109 and 239) the osteoid and completely decalcified tissues stain yellow to red, while the bone containing calcium, when hematoxylin is used in combination with carmine, stains blue. The use of Mueller's solution for distinguishing the so-called osteoid tissue from the bone containing calcium is best applicable in the case of pathologic bone such as that seen in osteomalacia, rickets and the fibrous osteodystrophias.

Recently, Bock<sup>29</sup> described a hematoxylin method for distinguishing osteoid tissue, useful for tissues decalcified in von Ebner's fluid or nitric

29. Bock: Ztschr. f. wissenschaft. Mikr. **40**:318, 1923.

acid. Bone is placed for from one to four weeks in a solution of four parts 10 per cent solution of solution of formaldehyde and one part Mueller's fluid. Decalcification in von Ebner's solution or nitric acid is followed by neutralization and washing of the tissues in the usual manner. The author then preferred slow embedding in celloidin, though paraffin may be used. The method of staining as given by Bock is as follows: Sections are stained for from twelve to eighteen hours in Hansen's hematoxylin, which must be prepared fresh each time. It is made of three solutions: (1) 1 Gm. of hematoxylin dissolved in 10 cc. of absolute alcohol, (2) 20 Gm. of potassium alum dissolved in 200 cc. of distilled water and (3) 1 Gm. of potassium permanganate dissolved in 16 cc. of distilled water. Solutions 1 and 2 are mixed and 3 cc. of solution 3 is added. The mixture is boiled for one minute. When cool it is filtered and is then ready for use. Strongly overstained sections are differentiated in a mixture of equal parts of pure glycerin and glacial acetic acid for from five to twenty minutes or longer, and then washed in running water for an hour. Sections are counterstained for five minutes in alcoholic eosin, four parts eosin to 1,000 cc. of 95 per cent alcohol. They are dehydrated, cleared and mounted in Canada balsam.

By this method, the osteoid tissue stains red, while the bone containing calcium stains a deep blue. This method is recent. Confirmations of its usefulness have not appeared in the literature.

#### CONCLUSION

The methods given are all tried procedures that have been found useful in studying bone from all angles. The choice of a method for the study of bone is conditioned by the purpose of the examination. The pathologist is most handicapped in the study of bone since the diagnosis of a lesion in bone rests mainly on the cellular elements and these are the structures most injured by decalcifying agents. The pathologist frequently need not use compact bone to make a diagnosis so that he may not have to decalcify the tissue or may be able to use Mueller's fluid. However, if decalcification is necessary, rapid treatment with nitric acid, though not entirely satisfactory, is the best procedure. Histologists, studying the structure of bone, are not confronted by this difficulty.

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#### CORRECTION

In the article by Dr. Stacy R. Mettier, entitled, "The Structural Changes of the Liver in Pernicious Anemia: A Contrast Between Relapse and Remission," in the August issue (*ARCH. PATH.* 8:213, 1929), the word "hyperatrophy," in the first conclusion in the Summary on page 222 should read "hypertrophy."

## Notes and News

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**University News, Promotions, Resignations, Appointments, Deaths.**—William T. Belfield, pioneer in genito-urinary surgery and one of the first American students of bacteriology, has died at the age of 73. Dr. Belfield delivered the Cartwright Lectures in New York in 1883, which were republished in book form under the title, *On the Relation of Micro-Organisms to Disease*.

The American Society for the Control of Cancer, 25 West Forty-Third Street, New York, has announced that Robert B. Greenough, assistant professor of surgery, Harvard Medical School, has become the chairman of its board of directors, and that Clarence C. Little, director of the Jackson Memorial Laboratory, Mount Desert Island, Me., has been appointed its managing director.

The Institute of Pathology (Howard T. Karsner, director) at Western Reserve University, Cleveland, was dedicated with appropriate ceremonies on October 7. The dedicatory address was given by Henry R. Dean, professor of pathology in Cambridge University, England.

**A Central Bureau for the Study of Tumors in Philadelphia.**—This bureau has been organized by Dr. Joseph P. McFarland, who acts as its director without pay. The bureau was established by the aid of Dr. George M. Dorrance, who underwrites the expenses for the first year, and of Dr. Stanley P. Reinmann, who obtained the use of the former pathologic laboratory of the Lankenau Hospital for the use of the bureau. The bureau is a strictly independent enterprise which begins by undertaking (1) to collect microscopic specimens of all tumors treated in all the hospitals of Philadelphia and vicinity, together with full data regarding each; (2) to identify, classify and make this material available to all scholars desiring to use it for research or comparison; (3) to follow up each case of malignant tumor until the death of the patient; (4) to use the data and specimens for study and publication, and (5) to collect and maintain a library of books and pamphlets on tumors and an index to the literature. In addition, it is intended that the bureau shall concern itself with larger problems and with the collection of data that may throw a light on fundamental questions.

Membership in the bureau is free to all pathologists, surgeons and roentgenologists who deal with tumors, without other obligation than the contribution of such material and data as they may have which will be collected by messenger from the bureau. It is expected that the Philadelphia Health Council will undertake the follow-up of patients suffering from malignant tumors.

The bureau is not in any sense a private laboratory in which tumors are diagnosed on application. It offers its benefits to its members without cost and will be conducted in the interest of science.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

INFLUENCE OF EXPERIMENTAL HYPERTHYROIDISM ON GESTATION. M. M. KUNDE, J. CARLSON and T. PROUD, *Am. J. Physiol.* **88**:747, 1929.

In severe hyperthyroidism induced in cretin rabbits there was observed an apparent increase in the number of developing graafian follicles and primordial ova. In rabbits with severe induced hyperthyroidism, the processes of estrus, ovulation, fertilization, migration and implantation took place, but the young were seldom born, resorption of the fetus taking place usually during the latter two thirds of pregnancy.

H. E. EGGERS.

THE BLOOD PLASMA OF NORMAL AND PARATHYROIDECTOMIZED ALBINO RATS. W. R. TWEEDY and S. B. CHANDLER, *Am. J. Physiol.* **88**:754, 1929.

In normal white rats, on a standard diet, the blood calcium varied between 9.25 and 12.5 mg. per hundred cubic centimeters. This value was not altered by unilateral parathyroidectomy, but on removal of the second parathyroid there was a temporary drop below the low normal value. This abnormal level persisted for a few weeks only. The drop occurred suddenly in some cases, rather slowly in others. By the end of 100 days, there was a definite tendency of the blood calcium to rise, and by the end of from 200 to 300 days, it may have attained a value just below low normal. Parathyroidectomized rats are from two to three times as reactive to comparable amounts of parathyroid hormone as are normal animals.

H. E. EGGERS.

A NEW DEFICIENCY DISEASE PRODUCED BY THE RIGID EXCLUSION OF FAT FROM THE DIET. G. O. and M. M. BURR, *J. Biol. Chem.* **82**:345, 1929.

A new deficiency disease, involving caudal necrosis, has been observed in rats maintained on diets extremely low in fat. Although the nonsaponifiable and glycerol fractions of fat appear to be ineffective in curing the disease, it has been entirely cured following the addition of 2 per cent of fatty acid to the fat-free ration.

ARTHUR LOCKE.

RELATION OF OESTRUS HORMONE TO NYMPHOMANIA OR PERSISTENT ESTRUS OF COWS. W. FREI and E. LUTZ, *Virchows Arch. f. path. Anat.* **271**:572, 1929.

Frei and Lutz devote thirty-seven pages to a critical review of the literature relating to the estrus hormone. Of the various substances that have been described as having an estrus-producing action, they consider that only the follicle fluid or the cells of the follicle wall contain the true hormone. They doubt that true and complete estrus has been caused by some of the substances used. The occurrence of the hormone in the corpus luteum and placenta, as described by many, is paradoxical. The authors believe the corpus luteum absorbs, stores and renders inactive the hormone formed by the follicle. Nymphomania of cows is a condition of persistent sexual desire or estrus. Manual rupture through the vagina of an enlarged ovarian follicle sometimes overcomes the condition. The vaginal smear of nymphomaniac cows contained epithelial cells and leukocytes, but no hornified epithelia. The authors conclude that nymphomania is due to the persistence of unruptured follicles in the ovary; since no corpora lutea are formed, the follicle hormone acts continuously. Nymphomania may go into anaphrodisia when the ovary becomes completely cystic or atrophic.

O. T. SCHULTZ.

EFFECT OF BLOCKAGE OF RETICULO-ENDOTHELIAL SYSTEM ON LEVEL OF BLOOD SUGAR. E. J. STERKIN and E. L. KLERNER-POSCHENJAN, *Ztschr. f. d. ges. exper. Med.* **64**:311, 1929.

A single intravenous injection (dogs) of india ink, vitargol or collargol generally did not affect the level of the blood sugar. After chronic, intensive blockage of the reticulo-endothelial system with the substances named, no change of level in the blood sugar beyond normal variation was obtained. Splenectomy with chronic blockage likewise was without effect. (These results are contrary to experiments reported by F. Venulet, and abstracted in this journal.)

BALDUIN LUCKE.

EFFECT OF RAREFICATION OF THE AIR ON NUMBER OF ERYTHROCYTES AND HEMOGLOBIN CONTENT OF NORMAL AND OF SPLENECTOMIZED ANIMALS  
G. GIANNINI, *Ztschr. f. d. ges. exper. Med.* **64**:431, 1929.

Experiments were undertaken to decide whether the increase in the number of erythrocytes due to rarefaction of the air is absolute or relative. If the increase is absolute, a number of erythrocytes must rapidly be destroyed on the return to normal air pressure, since, shortly after, the person or the animal used in the experiment presents normal values. Rarefaction of the air was accomplished in a Loewy chamber; rabbits, guinea-pigs and rats were used. The number of erythrocytes increased from 3,000,000 to 3,500,000 per cubic millimeter above the normal after an exposure of from seventy-two to thirty-six hours to rarefied air (300 to 350 mm. of mercury). Polychromatophilia, anisocytosis and poikilocytosis occurred. On a return to normal air pressure, the erythrocyte counts quickly regained a normal level (often within forty-eight hours). The increase in hemoglobin content lagged behind the increase in the number of erythrocytes in the rats and the guinea-pigs, but paralleled that in the rabbits. Conversely, after the return to normal pressure, the increase in hemoglobin content persisted for a somewhat longer period than did the increase in number of erythrocytes. Rarefied air brought about a decrease in color index in rats and guinea-pigs, but not in rabbits.

In splenectomized animals, rarefaction of air led only to a slight increase in the red cell count, but to a relatively greater increase in hemoglobin (both absolute and relative). The color index rose above 1 and remained at this level even six hours after the exposure. Destruction of red cells following the return to normal air pressure after exposure to rarefied air manifested itself by bilirubinemia, which appeared within twenty-four hours following exposure.

BALDUIN LUCKE.

LEUKOCYTOSIS AFTER BRAIN PUNCTURE. G. ROSENOW, *Ztschr. f. d. ges. exper. Med.* **64**:452, 1929.

Brain puncture (in rabbits) involving the corpus stratum, the thalamus or the hypothalamic region promptly leads to neutrophilic leukocytosis. There is no relation between the degree of puncture fever and the leukocytic curve. Puncture of other regions of the brain does not induce leukocytosis.

BALDUIN LUCKE

### Pathologic Anatomy

THE MICROSCOPIC ELEMENTS IN BILE EDWARD HOLLANDER, *Am. J. M. Sc.* **177**:371, 1929.

Microscopic examination of bile from the gallbladder and bile ducts reveals four elements diagnostic of pathologic states of the biliary tract: bile flocculi, intensely bile-stained debris, agminated cholesterol crystals and sandlike particles

PEARL M. ZIEK

PRIMARY MULTIPLE SARCOMATOSIS OF THE SKIN. W. C. HUEPER and B. B. BEESON, Arch. Dermat. & Syph. **19**:794, 1929.

The clinical course and postmortem examination of a patient with multiple sarcomatosis are reported. The authors believe the neoplasm to be mesodermal and to belong to the group of primary, multiple round cell sarcomas of the skin. The exact origin is doubtful. The dense accumulations of tumor cells around vessels and nerves suggest that these tissues were the primary foci.

FRANK M. COCHEMS.

OCCURRENCE OF ACCESSORY PARATHYROID GLANDS. W. L. A. WELLBROCK, J. A. M. A. **92**:1821, 1929.

The parathyroid glands found in this series were situated anywhere on the anterior surface, on the isthmus or on the lateral surface, and a few were embedded in the thyroid tissue, just within the edge of the thyroid gland. One or more parathyroid glands were found in 7.76 per cent of the 1,056 thyroid glands examined. These were all checked by microscopic examination. The parathyroid glands are finely granular, soft, yellowish brown, lenticular, spheroidal or pear-shaped structures, from 2 to 10 mm. in diameter. Parathyroid glands are often confused with accessory thyroid glands, lymph nodes, hemolymph glands and lobules of fat. This is the chief reason for the failure of transplants. Parathyroid glands were found in equal numbers on exophthalmic, adenomatous and colloid goiters. The largest gland on which a parathyroid gland was found was adenomatous, weighing 275 Gm.; the smallest was a hypertrophic parenchymatous gland weighing 8 Gm. In two cases, three parathyroid glands were found, in one of which the three were in a cluster. In three cases, two were found, and in two cases one was on each lobe of the thyroid gland. In only one case was there mild transitory tetany following thyroidectomy.

AUTHOR'S SUMMARY.

PERINEPHRITIC ABSCESS. A. H. PEACOCK, Surg. Gynec. & Obst. **48**:757, 1929.

Suppurative processes in the perirenal tissue were regarded as being of renal or extrarenal origin, and the usual methods of infection were considered. Twenty-one cases are reported by the author. In four of renal origin, the process was secondary to cystitis in one, and to prostatic hypertrophy in one, and in two it was due to calculi in the ureters. In three of ten cases the perinephritic abscess followed furuncles, in four the condition was associated with pregnancy, in one each it followed tonsillitis and appendiceal abscess, and in one it was concomitant with actinomycotic suppuration that resulted in perforation of the duodenum and colon with resultant invasion of the tissues about the right kidney. In the remaining seven patients the etiology could not be determined. Bacteriologic examination of the abscesses revealed staphylococci in fifteen, *bacillus coli* in two, streptococci and actinomyces in one, and in two the cultures were sterile. The urine in ten was sterile, but in seven *B. coli* occurred, staphylococci were found in three, and streptococci in one. In almost all patients the abscess resulted in bulging in the costo-vertebral angle, in the abdomen or in the region of Poupart's ligament.

RICHARD A. LIEVENDAHL.

CECAL DIVERTICULOSIS, WITH SPECIAL REFERENCE TO TRAUMATIC DIVERTICULI. L. A. GREENSFELDER and R. I. HILLER, Surg. Gynec. & Obst. **48**:786, 1929.

Diverticuli of the cecum may follow appendectomy as the result of eversion of the bowel between constricting bands of omentum, of traction by omental adhesions and of migration of purse-string suture material toward the lumen with subsequent defect in the wall, or the circular muscle may be injured with resultant weakness of the cecal wall; in other instances the insufficiency may be caused by intramural abscesses. The material studied was obtained from two cases in which the patients were operated on and from two more of a series of 400 autopsies. In this number

of necropsies twenty-three of the bodies had had their appendixes removed. In addition appendectomy was performed in thirteen dogs. In the six animals in which the purse-string suture method was done, the percentage of these types of complications was more frequent than in the other seven in which the ligature-drop procedure was used.

RICHARD A. LIFVENDAHL.

PULMONARY ASBESTOSIS. W. BURTON WOOD, *Tubercle* **10**:358, 1929.

The author reports on fifteen cases of pulmonary asbestosis, presenting some interesting roentgenograms as well as reviewing the chemical composition of asbestos fibers. He covers the pathology and symptoms as well as the physical signs, prognosis and duration of exposure to the dust. The article should be read in the original as it is not suitable for abstract.

H. J. CORPER.

THE CHANGES CAUSED BY TREATING GENERAL PARESIS WITH MALARIA. T. VON LEHOCZKY, *Arch. f. Psychiat.* **86**:443, 1929.

A study was made of twelve cases of general paresis in which ten of the patients were treated with malaria and two with milk injections. Both methods had the same effects. In evaluating the pathologic evidence, one must distinguish between those phenomena which belong to the "basic process" (general paresis) and those which may be the result of the inoculation. Another distinction is urged between the lasting and the transitory changes, both ectodermal and mesodermal. Among the lasting changes are classed: fibrous meningitis, destruction of ganglion cells and processes and the increase in glia (quantitative glia changes). The transitory changes are: the inflammatory infiltration, the pathologic modification of the ganglion cells (as distinguished from their destruction), the myelin degeneration and the qualitative glia changes. It is concluded that malaria treatment has an effect on the transitory changes only. This dictum is in sharp contrast with the observation of Straeussler and Koskinas. These workers postulated a "healing inflammation" and interpreted their results as indicating a shift from the "malignant" type of inflammation (plasma cells) toward the "benign" type (lymphocytes). Aside from this shift, they noticed an "allergic change" to the effect that the non-specific paretic process gave way to a specific gummatous appearance. Lehoczky denies both these claims. Malaria works only on the mesodermal structures. Among the infiltrative elements many degenerative forms were found: karyorrhesis in the lymphocytes and vacuole degeneration in the plasma cells. W. Freeman claimed a restitution of the disturbed lamination of the cortex. This "conspicuous exaggeration of the theory of Straeussler and Koskinas" is energetically rejected.

A. A. LOW.

ABSCESS OF THE LUNG OF TEN YEARS' DURATION. E. SCHLÜTER, *Centralbl. f. allg. Path. u. path. Anat.* **45**:6, 1929.

A man, aged 56, died immediately after exploratory puncture of an empyema cavity which had drained occasionally since its formation ten years previously. At autopsy, the left upper pulmonary lobe was found transformed into a cavity containing about 600 cc. of creamy pus. The lining of this cavity was of flat epithelium except in some depressions and projections where it was cuboidal or cylindric; occasional zones of granulations indicated recent inflammation. No communications with bronchi were demonstrable, drainage having taken place from the lung into the empyema sac and from this through the fistula to the outside.

GEORGE RUKSTINAT.

CALCIFICATION OF THE VASA DEFERENTIA. W. DOPHEIDE, *Centralbl. f. allg. Path. u. path. Anat.* **45**:39, 1929.

Calcification of the vasae deferentiae was found in two men, aged 80 and 77, respectively. In both the process was limited to the middle circular muscle layer



and was accompanied by a connective tissue increase. In one instance, the process involved the entire circumference and had a length of 2.5 cm.

GEORGE RUKSTINAT.

NEPHRITIC RETINITIS. R. HANSSEN, *Klin. Monatsbl. f. Augenh.* **82**:40, 1929.

Nephritic retinitis does not arise as the result of a primary disturbance of the blood vessels but is essentially a toxic inflammatory process. In cases of nephritic retinitis showing changes in the heart and blood vessels together with increased blood pressure but with little decrease in kidney function, it cannot be demonstrated that the blood pressure is the cause of the retinitis. It is more probable that in such cases the injurious toxins which have produced the changes in the vascular apparatus have attacked the eyes earlier than the kidneys. The apparent thinness of the retinal blood vessels is not due to a contraction of the vessels or to ischemia, but is rather to be explained as a part of general anemia. From the latter there results a swelling and cloudiness of the tissues of the optic papilla which surround the vessel walls causing the retinal vessels to be less visible. The cystoid spaces in the retina occurring in nephritic retinitis are not filled with a simple serous transudate but with an inflammatory exudate rich in albumin and containing a fibrin network, fat and cells.

CHARLES WEISS.

CONGENITAL ANOMALY OF THE HEART. H. GERSTMANN, *Virchows Arch. f. path. Anat.* **271**:1, 1929.

The author describes a heart obtained from a new-born, full-term, female infant. It consisted of two auricles and a large ventricle, from which the pulmonic artery arose. The latter united with the aorta at the open ductus arteriosus. Separated from the main ventricular cavity by a perforated septum was a small cavity from which the aorta arose. This septum was not the true interventricular septum, but the persistent aorticopulmonic crest. The anomaly is considered a type IV in the classification of Spitzer, but is not characteristic of this type in that detorsion had been carried somewhat further than is the rule for Spitzer's type IV.

O. T. SCHULTZ.

STENOSIS OF CONUS ARTERIOSUS AND PULMONIC ORIFICE. L. SKUBISZEWSKI, *Virchows Arch. f. path. Anat.* **271**:14, 1929.

A man, aged 54, had been under medical care for cardiac decompensation at various times since 1922. He had always been cyanotic. The clinical diagnosis was mitral stenosis. Death occurred suddenly. He had been free from edema for some time previous to death. The heart weighed 600 Gm., the hypertrophy being chiefly of the right ventricle. The root of the pulmonic artery appeared slightly narrower than normal. The lumen of the conus arteriosus was diminished to 1.2 cm. in diameter. The segments of the pulmonic valve were fused and formed a funnel-shaped structure with an opening 4 mm. in diameter. The subaortic portion of the ventricular septum was defective. The lungs received their main supply of blood through a branch given off from the left subclavian artery.

O. T. SCHULTZ.

RHACHISCHISIS WITH TRIPLICATION OF THE SPINAL CORD. R. ALTSCHUL, *Virchows Arch. f. path. Anat.* **271**:45, 1929.

The condition which the author reports occurred in a girl, aged 9 months, who had mongoloid characteristics and was psychically subnormal. Muscular movements and plantar and knee reflexes were normal. The arm reflexes could not be elicited. In the cervical region was a fluctuant mass which measured 22 cm. in cross diameter by 7 cm. in height. Pressure on the mass caused convulsive movements. At necropsy, the laminae of the last three cervical and first dorsal vertebrae were absent. The cavity of the mass seen externally was lined by dura and com-

municated with the subdural space in the region of the vertebral defect. In this region the spinal cord was divided longitudinally into three parts. The left portion was fairly complete, the right and middle portions being somewhat more rudimentary. Each portion was surrounded by leptomeninges. The three portions united again at the level of the fifth dorsal vertebra, from which point downward the cord was normal. The author believes that this is the only recorded instance of longitudinal division of the cord into three parts. The embryogenetic explanation is difficult. He believes that the anomaly was due to inrolling of the dorsal medullary plates, which process was complete on the left and led to the formation of a complete left cord. The process was less complete on the right side and subdivided the original right cord into two parts.

O. T. SCHULTZ.

OSTEOSCLEROTIC ANEMIA WITH RETICULO-ENDOTHELIAL PROLIFERATION.

A. A. WASILJEFF, *Virchows Arch. f. path. Anat.* **271**:134, 1929.

A man, aged 30, had complained for five years of pain in the lower extremities along the bones, not associated with swelling of the joints. The bones of the upper extremities also became painful during the latter course of his illness. He had had hemorrhages from the nose and urinary tract. He entered the hospital in a moribund condition. He was undernourished and anemic. Hematologic examination revealed 1,200,000 erythrocytes, 35 per cent hemoglobin, 11,450 leukocytes and 28,000 platelets. Anisocytosis, poikilocytosis, normalblasts and myelocytes were noted. The spleen was moderately enlarged. In all the bones examined post mortem, the marrow was replaced by pale tissue, which on microscopic examination consisted of large, ovoid cells derived from the vascular endothelium. This tissue had replaced the hematopoietic tissue with the exception of small groups of lymphocytes. Large cells of similar type were present also in the liver and spleen, and in the lungs they occurred in the form of small groups in the septums outside the capillaries, their position suggesting an origin from adventitial cells. They were present in the bronchial lymph nodes, but not in the other lymph nodes. The cells were suggestive of Gaucher cells, but did not have the characteristic morphology or staining reactions. They contained inclusions which had the staining reaction of mucoprotein. Microchemical staining reactions for lipoids were negative. Myelopoiesis was present in the liver and spleen. The author interprets the case as a metabolic disturbance associated with proliferation of the reticulo-endothelial system, which had led to replacement of the hematopoietic tissue of the bone marrow, where the reticulo-endothelial proliferation was combined with fibrosis.

O. T. SCHULTZ.

HEMATOLOGIC EFFECTS OF EXPERIMENTAL BENZENE ADMINISTRATION. G. ORZECOWSKI, *Virchows Arch. f. path. Anat.* **271**:191, 1929.

Subcutaneous administration of benzene in rabbits causes no change in the erythrocytes or platelets, only a slight change in the lymphocytes, decreases the coagulation time and has its most marked effect on the granulocytes, which are apparently specifically destroyed.

O. T. SCHULTZ.

CHANGES IN THE SPLEEN IN MALARIA. B. A. PHOTAKIS, *Virchows Arch. f. path. Anat.* **271**:192, 1929.

The author divides the cases of malaria in which he has been able to study the spleen post mortem into acute cases in which death was caused by malaria, chronic cases in which death was due to malaria and chronic cases in which death was due to some other cause. The acute cases are subdivided into those which run a short, hyperacute, highly toxic course with hyperpyrexia and extreme destruction of erythrocytes. In such cases the spleen may measure 40 by 20 by 18 cm. and weigh as much as 1,200 Gm. It is soft, brownish black and almost diffuent on section. The size is due chiefly to engorgement. The hyperplasia present is limited to the sinus endothelium, which exhibits marked phagocytosis of

injured red blood corpuscles. In a second group of acute cases the course is more prolonged, lasts from six to eight weeks and death is due to the malarial infection. In such cases the spleen is also greatly enlarged, is slightly firmer and is a grayish black or grayish red. In such spleens reticular hyperplasia is associated with sinus endothelial hyperplasia and predominates over the latter. In chronic cases the spleen shrinks and becomes firmer, and the chief hyperplastic change occurs in the connective tissue framework of the organ.

O. T. SCHULTZ.

**PATHOLOGY OF SUPRARENAL.** E. OMELSKYJ, *Virchows Arch. f. path. Anat.* **271**:377, 1929.

Kovács, of Vienna (*Beitr. z. path. Anat. u. z. allg. Path.* **79**:213, 1928), had described, in a patient with Addison's disease, a condition of bilateral disappearance of the suprarenal cortex, the medulla being spared. Kovács termed the condition cytotoxic cortical contraction of the suprarenal gland and held the pathologic changes of the suprarenal gland to be the result of some toxic substance which acted specifically over a long period of time on the cortical cells. The present author, stimulated apparently by Kovács and working under the direction of Erdheim, attempts to establish more firmly the conception of specific cytotoxic destruction of the suprarenal cortex. The chief basis of his paper of fifty-five pages is a case of hypophyseal cachexia, in which the suprarenal glands showed the kind of change described by Kovács. The case, described clinically and microscopically in great detail, is placed in the group termed multiple sclerosis of the endocrine organ by Falta. There were no symptoms of Addison's disease. The chief symptomatology was ascribed to loss of function of the hypophysis, which was found at necropsy to be small and fibrotic. Terminal evidences of myxedema were held to be due to the fibrotic thyroid, and the early menopause to premature sclerosis of the ovaries. The cortical injury in the suprarenals, which was systemic and not local in origin, occurred late; hence, definite evidences of Addison's disease were not present. By comparison of the microscopic changes of the suprarenals in this case with those of other forms of contraction of the suprarenal, the author attempts to establish histologic criteria which will permit differentiation of suprarenal atrophy of systemic origin, that is, cytotoxic contraction, from atrophy due to causes acting locally, such as infection, thrombosis and tuberculosis.

O. T. SCHULTZ.

**ACUTE PLACENTITIS.** W. LAUBSCHER, *Virchows Arch. f. path. Anat.* **271**:450, 1929.

The author reports a case of placental infection, followed by sepsis and death of the patient; it was possible to study both the placenta and the uterus in this case. In a second case only the placenta could be studied. In each case, rupture of the membranes had occurred early and labor was protracted. The organisms gained entry from below, penetrating at the margin of the placenta, and spreading beneath the fetal membrane surface. Freedom of the intervillous spaces from inflammatory reaction is evidence that the infection was not hematogenous in origin.

O. T. SCHULTZ.

**HYPERTROPHIC PULMONARY OSTEOARTHIROPATHY.** C. CRUMP, *Virchows Arch. f. path. Anat.* **271**:467, 1929.

Crump, of Boston, presents from Erdheim's institute a detailed study of a case of hypertrophic pulmonary osteo-arthritis, for which he prefers the name generalized osteophytosis, which is interesting because the case was closely followed clinically. The patient was a woman, aged 50, whose breast had been amputated for carcinoma in 1923. A year and a half later she returned to the hospital, where she remained for over a year. Fifteen months before death, following a slight, febrile pharyngitis, swelling of the dorsum of the foot and pain in the small joints of the foot, hand and fingers caused her to return to the hospital. In

time, the elbows and knees became painful. Involvement of the left lung was evident when she entered the hospital because of the joint pains; a roentgenologic diagnosis of secondary carcinoma of the lung was later made. Hypertrophy and osteophytosis of the bones was evident roentgenologically at examinations made eight and three months before death. The fingers became clubbed. The patient presented the three classic manifestations of the Bamberger-Marie syndrome, namely, hypertrophy and osteophytosis of the bone, involvement of the joints and clubbing of the fingers. Of these, the changes in the bone are the only ones which are characteristic. They may occur alone, but permit the diagnosis; the arthritis or clubbing of the fingers may occur alone, diagnosis being impossible, or either may be combined with the lesion of the bone. The microscopic changes of the bones are described in detail and are illustrated by numerous photomicrographs. The process is essentially one of subperiosteal bone formation, in the form of broader plates and of osteophytic excrescences. The process appears to be periodic, the new bone being laid down in lamellae or laminae. The bone is porous, but would probably become more condensed with longer duration of the disease. The involvement of the joints consists of a chronic arthritis and synovitis. Crump believes that the disease is due to a toxin of unknown nature, which is liberated in diseases of the lung and heart, more rarely of the liver or lymph nodes. The toxin may attack the bones, the joints and the soft tissues about the terminal phalanges of the fingers, or only one or two of these situations may be attacked. Four closely printed pages of bibliographic references conclude the article.

O. T. SCHULTZ.

CIRCULATORY SYSTEM OF DICEPHALIC MONSTER. OLGA SEAMON, Virchows Arch. f. path. Anat. **271**:512, 1929.

In the monstrosity studied, the heads were separate, the vertebral columns were separate down to the sacrum, the internal organs were duplicated with the exception of the urinary bladder and the two livers were fused. Especial attention was given to study of the circulatory system, since the heart of one-half was rudimentary and had no connection with the vascular system of its portion. The relations of the two circulatory systems are described in detail, and the embryogenesis of the cardiovascular anomaly is discussed.

O. T. SCHULTZ.

HISTOLOGY OF CHONDRODYSTROPHIC CHICK EMBRYOS. W. LANDAUER, Virchows Arch. f. path. Anat. **271**:534, 1929.

Histologic study of the endocrine organs of chondrodystrophic chicks, removed from the shell on the twenty-second day of incubation, failed to reveal any changes which might be correlated with the chondrodystrophic condition. The only change noted was somewhat delayed differentiation of all the endocrine organs, as compared with normal embryos of the same age.

HISTOLOGIC LESIONS IN EARLY DIFFUSE GLOMERULONEPHRITIS. R. HUECKEL, Virchows Arch. f. path. Anat. **271**:211, 1929.

The patient died thirty hours after the sudden onset of the disease. There were small, irregular, oblong, dark red spots on the cut surfaces of the kidneys. The brain was edematous. The circular edema around the vas afferens and the swelling and vacuolization of its walls were found only in a few glomeruli. They are considered secondary to the combined glomerulonephritic and glomerulonephrotic changes as presented by the kidneys in this unusually early case. They cannot be the first lesion in glomerulonephritis.

ALFRED PLAUT.

DEXTROVERSION, INVERSION AND TRANSPOSITION OF THE HEART. A. SPITZER, Virchows Arch. f. path. Anat. **271**:226, 1929.

Spitzer dedicates his seventy-eight page monograph to Professor Julius Tandler, the anatomist, in honor of the latter's sixtieth birthday. The article is based on a heart obtained from a boy who died at the age of 6 years and who had been

cyanotic from birth. The first third is a minutely detailed description of the changes found, the remainder consisting of a discussion of the factors involved in the genesis of the malformation. The latter appeared at first glance to be a simple dextroversion, but closer study revealed that both inversion and transposition were concerned in bringing about the anomaly. The heart had a large, hypertrophied right ventricle with, however, a typical mitral valve. The left ventricle was small and had a typical tricuspid valve. The ventricular septum was defective, the defect beginning in the subaortic region and part of the margin of the defect being formed by the aorticopulmonic crest. The ductus Botalli was patent, and the foramen ovale was open. The smaller left ventricle (transposed right) gave rise to the aorta, which was situated to the left, and the pulmonary artery, which was to the right and was atretic in its intramuscular or conus portion. The malformation is discussed as a possible atavistic reversion to a stage in ontogenetic or phylogenetic development, and the relation of dextroversion, inversion and transposition to each other and the possible combinations of these processes are elaborated in detail.

O. T. SCHULTZ.

UREMIC DERMATITIS. R. ROESSLE, *Virchows Arch. f. path. Anat.* **271**:304, 1929.

Among twenty-nine autopsies of uremia cases, skin lesions were found in twenty-four. Kidney disease without uremia does not seem to make skin lesions. The skin lesions in uremia are not characteristic. Coats of lymphocytes around the blood vessels (upper layer) are found most frequently. Only in severe cases are the epidermis and the deeper layers of cutis affected. Swelling of endothelium occurs and the walls of capillaries may become indistinct. Leukocytes, plasma cells and mast cells were missing; eosinophilic leukocytes were found once. Small necroses occur in the connective tissue of the cutis. Degenerative changes in the epithelium (ballooning degeneration) were marked in the skin of an old painter, with extreme arteriosclerotic atrophy of the kidneys. This lesion is similar to herpes zoster, and it was in the skin of this same patient that perineural inflammation was found. The mechanism of the formation of the skin lesion is unknown since it is not known what uremia is. The amount of urea in the skin, however, was found fairly well in ratio to the degree of the skin lesion.

ALFRED PLAUT.

REACTION OF FIXED TISSUES TO INFECTION. G. MEYER, *Virchows Arch. f. path. Anat.* **271**:317, 1929.

The literal translation of the title of this article is "Connective Tissue and Foreign Body." The foreign bodies, the effects of which were studied, were micro-organisms, chiefly staphylococci, which enter the skin by way of the hair follicles and caused furuncles. The reaction set up in the subdermal tissue is a progressive and continuing one, differing in this respect from that caused by nonliving foreign bodies. In the interpretation of the changes which occur, the conception of von Mellendorf is accepted. The supporting connective tissue is looked on as a syncytium or plasmodium, composed of living cells capable of reproduction and of fibrils which cannot reproduce themselves. The syncytium is transformed into a multipotent mesenchyme when its cells are stimulated to proliferation. The entrance of the foreign micro-organism causes degeneration and destruction of the nonreproducible collagenous and other fibrils. The cells, stimulated to amitotic division, give rise to multipotent mononucleated cells, which become transformed into lymphocytes, granular leukocytes and phagocytic histiocytes. These cells, the exudate cells supposedly derived from the blood stream according to the older conception of inflammation, are held to arise chiefly locally from the fixed tissue. A point which is emphasized is their origin by amitosis. Mitosis, when it occurs, as it does after the process is established, leads to new formation and regeneration of the fixed tissues, not to wandering cells.

O. T. SCHULTZ.

EFFECT OF DIFFERENT KINDS OF COAL DUST ON THE LUNGS. H. BORCHARDT, *Virchows Arch. f. path. Anat.* **271**:366, 1929.

Belief that pigmentation of the lungs due to carbon particles results from inhaled material dates back to Pearson, in 1813. The doctrine of the inhalational pigmentation of the lungs was denied by Virchow, but was, of course, later established again as correct. Of the various kinds of foreign material which are inhaled, coal or carbon dust appears to be least irritating and to cause least reaction in the lung. Differences in the degree of reaction to coal dust, however, have been noted in different localities and have led to controversy as to the innocuousness of coal dust. Borchardt believed that physical and chemical differences in the inhaled coal might be responsible for differences in tissue reaction and put the matter to the experimental test by subjecting rabbits to the inhalation of dust-laden air for one hour daily. The materials used were soot, animal charcoal, hard coal or anthracite and soft coal. Microscopic examination revealed distinct differences in the degree of fibrosis, this being greatest after inhalation of soft coal dust, less after hard coal and slight after animal charcoal, with practically no reaction after soot. The degree of self-cleansing of the lung was in inverse order to the degree of tissue reaction. The differences noted in the lungs of the experimental animals were comparable to those seen in the lungs of human beings.

O. T. SCHULTZ.

TERATOMA OF THE HYPOPHYSEAL REGION WITH REFERENCE TO SUPRARENALS IN ANENCEPHALY. E. J. KRAUS, *Virchows Arch. f. path. Anat.* **271**:546, 1929.

An otherwise well formed prematurely born girl, 42 cm. long, had a teratoid tumor which protruded into the cavum cranii and into the pharynx; the canalis craniopharyngeus was wide. The brain was normal. The anterior lobe of hypophysis was found on the posterior aspect of the cranial part of the tumor; it was compressed but normal. Rathke's cysts and posterior lobe were absent. The suprarenal glands were normal. Therefore, one cannot assume that in anencephaly the defect of the suprarenal glands is due to absence of the posterior lobe of hypophysis.

ALFRED PLAUT.

MORPHOLOGY OF LYMPHADENOID TISSUE. J. WÄTJEN, *Virchows Arch. f. path. Anat.* **271**:556, 1929.

This is a contribution to the nature of the so-called germinal centers of the lymph nodes. Because of the lability of the lymphoid tissues it is necessary, in order to understand the normal variations, to study nodes from various regions of the same body, nodes at different age periods and nodes from persons in varying nutritional states. The author believes that the germinal center of Flemming or the secondary follicle of Heilmann is entirely connective tissue in origin, and that it results from atrophy or disappearance of lymphoid cells with their replacement by proliferated stroma cells. The author does not think it has been established that these cells can take on lymphoblastic properties.

O. T. SCHULTZ.

DOES THE CAPILLARY ENDOTHELIUM OF THE HYPOPHYSIS BELONG TO THE RETICULO-ENDOTHELIAL SYSTEM? GUSTAV SINCKE, *Ztschr. f. d. ges. exper. Med.* **63**:223, 1928.

Because of their common function of producing reticulum and of lining sinusoidal blood and lymph spaces, Aschoff grouped the capillary endothelium of the hypophysis with the reticulo-endothelial cells of the sinuses of the lymph nodes, the blood sinuses of the spleen, the capillaries of the liver (Kupffer's cells), the capillaries of the bone marrow and the suprarenal cortex. On the basis of an extensive series of experiments on rats (and in a few cases on rabbits) with fifteen different dyes and many other substances in the colloidal state, Sincke came

to the conclusion that the capillary endothelium of the rat should not be grouped with the cells of the reticulo-endothelial system in the restricted sense of the word. While the colloidal metals, carbon, arsphenamine, etc., were stored by the Kupffer cells and other reticulo-endothelial elements, the endothelial cells of the hypophysis did not generally take them up. Small quantities of some of the dyes were stored by the capillary endothelium of the pars intermedia.

DIFFUSE INTESTINE-LIKE ADENOMA OF THE RENAL PELVIS. ALFRED PLAUT, *Ztschr. f. urol. Chir.* 26:562, 1929.

A woman, aged 57, developed a fistula and a swelling at the site of operation after removal of a kidney stone. The kidney consisted of a flabby cystic structure the walls of which were lined with what seemed to be large intestine at first sight. There are mucus-producing glands, and there is much lymphatic tissue and a considerable amount of muscle. Part of the muscle can be traced to the muscularis of large blood vessels. Few glomeruli are preserved, but there is a considerable number of mostly narrow tubuli. In spots "embryonic kidney blastema" is found. The piece of ureter which was removed with the kidney is also lined with mucus-producing glands, but there is no overgrowth of muscle in it. This tumor cannot be classified; it is different from the tumor-like lesions in ectrophy of the bladder.

AUTHOR'S SUMMARY.

### Microbiology and Parasitology

MORPHOLOGIC AND BIOLOGIC STUDIES OF THE SPECIES OF *DIPHYLLOBOOTHRIUM* IN CHINA. ERNEST CARROLL FAUST, HORACE E. CAMPBELL and CLAUDE R. KELLOGG, *Am. J. Hyg.* 9:560, 1929.

The literature on infections with *Diphyllobothrium* in the Orient, particularly with *Sparganum mansoni*, and on the experimental development of adults from spargana in man and other vertebrates is critically reviewed. The results of a study of material collected from various vertebrate hosts in China are presented. The following species, all from China or its environs, are described: *Diphyllobothrium decipiens*, *D. mansoni*, *D. ranarum*, *D. erinacei*, *D. houghtoni* n. sp. *D. okumurai* n. sp. *D. latum* and *D. cordatum*. A discussion of the general characteristics of the genus *Diphyllobothrium* is presented, in which it is found desirable to divide the genus into two subgenera, *Diphyllobothrium* sensu stricto and *Spirometra* n. nom., on the basis of a rosetted outer uterine mass and eggs with rounded ends in the former subgenus, and a spirally piled outer uterus and eggs with roundly pointed ends in the latter subgenus. The type species of the genus is designated as type of the subgenus *Diphyllobothrium*, while the species *decipiens* is designated as type for the subgenus *Spirometra*. The experimental evidence which is reviewed confirms the subgeneric division. The distribution of the several species of *Diphyllobothrium* is outlined. The pathogenicity of the species of *D. decipiens* and *D. erinacei* is briefly presented.

AUTHORS' SUMMARY.

A CASE OF SPLENOMEGALY SHOWING PARATYPHOID BACILLI. HENRY EDMUND MELENEY, *Am. J. Trop. Med.* 9:97, 1929.

Under the name "tropical febrile splenomegaly" have been grouped a number of distinct diseases. One of these occurs outside the tropics, notably in North China in the neighborhood of Peking and Tientsin. A case of this kind is described in which a paratyphoid bacillus was isolated from the spleen at the time of splenectomy. Although the etiology in cases presenting this clinical picture may not always be the same, there is little doubt that it always involves a micro-organism the chief activity of which is in the spleen, with a secondary effect on the liver. Careful culturing of the blood of such patients, together with cultures of material from spleen and liver punctures, and of liver and spleen at the time of splenectomy, if carried out early in the disease, should yield important data on its etiology.

AUTHOR'S SUMMARY.

EPIDEMIOLOGY OF BLACKWATER FEVER IN SIAM. E. C. CORT, Am. J. Trop. Med. **9**:105, 1929.

Blackwater fever, before unknown in Siam, appeared in Chiangmai in epidemic form. The first epidemic was confined practically to one city block and to three family connections. The second epidemic occurred in a boy's school 4 miles from the city. A short time after the first epidemic, sporadic cases, twelve in all, began to appear. The evidence seems to point to a specific factor, supposedly a malarial parasite, but a variety capable of elaborating a potent hemolysin. Prevention of relapse in a series of cases with neoarsphenamine without quinine seems to suggest that this parasite is a variety of *Plasmodium vivax*. But it should be noted that these same observations from treatment alone might point to a spirochete or a leptospira.

AUTHOR'S SUMMARY.

PELLAGRA ASSOCIATED WITH ORGANIC DISEASE OF THE GASTRO-INTESTINAL TRACT. ROY H. TURNER, Am. J. Trop. Med. **9**:129, 1929.

The literature is briefly reviewed. The observations in a group of sixteen patients are presented in the form of a table. They all had pellagra and with it some organic disease of the gastro-intestinal tract. They represent 20 per cent of the patients studied. Symptoms of pellagra may obscure those of serious organic disease. The death rate in the group was high, 50 per cent dying in the hospital in spite of dietary treatment along most modern lines, as compared with 25 per cent in the control group. Two of the patients, one without diarrhea until after dermatitis had appeared, had been on an excellent diet throughout. The diet of four others was good up to the time the diarrhea appeared. The effect of such lesions on bacterial growth in the intestinal lumen and the absorption of harmful substances from the lumen is discussed. The suggestion is made that this may be an important factor in the production of the pellagra.

AUTHOR'S SUMMARY.

TUBERCULOUS LESIONS IN THE LUNG OF A NEGRO CHILD NINE WEEKS OLD. WILLIAM SNOW MILLER, Am. Rev. Tuberc. **19**:119, 1929.

A small tuberculous lymph node situated in the pleura, forming part of the boundary of an incisura interlobaris, with its afferent and efferent lymphatics is described. The focus from which tubercle bacilli were conveyed to the lymph node and the course of the lymphatics through which they passed were identified. Only in that portion of the lymph node which the lymphatic conveying the bacilli supplied were tubercles developed. The other lymphatics that entered the node formed a wide-open bypath through the node. The toxins contained in this bypath and in the associated sinuses gave rise to an intense hyperplasia of the lymphoid tissue in the remainder of the node. The lymph flow, as shown by the presence of numerous valves, was toward the pleura. This indicates that the direction of lymph flow described for other portions of the lung holds true in this situation; namely, that from a narrow zone around the periphery of the lung the flow is toward the pleura, while in other portions of the lung it is toward the hilum. Beyond the lymph node, the flow was through the pleural network of lymphatics to a hilum node, which showed active lesions. Lymphatics from other parts of the lung were seen entering the hilum node, showing that those described were not the only source from which it was infected.

H. J. CORPER.

TUBERCULOSIS OF THE COMMON CROW. CHARLES A. MITCHELL and R. C. DUTHIE, Am. Rev. Tuberc. **19**:134, 1929.

The incidence of tuberculosis in wild animals and birds in their natural state is largely a matter of conjecture and is governed in all probability by their relative chances of exposure rather than by any marked lack of susceptibility. In the case of *Corvidae* and birds of similar habits, contact with man and domesticated animals cannot be excluded. These birds might become infected in a number of



ways through contact with tuberculous poultry, domesticated animals and their dejecta, infected waste-products from garbage dumps and country slaughter-houses, and unburied carcasses of diseased animals. The susceptibility of *Corvidae* to mammalian tuberculosis is at present unknown. The ability of the crow to transmit infection to other birds or animals remains to be shown.

H. J. CORPER.

PREGNANCY AND PULMONARY TUBERCULOSIS. ARTHUR H. MORSE, Am. Rev. Tuberc. **19**:140, 1929.

Attention is called to the most common theories supporting the contention that the reproductive process as a whole deleteriously influences a coexistent pulmonary tuberculosis. The relevant outstanding clinical observations appearing in the literature of France, Germany and the United States during the past decade are reviewed. Certain factors are considered which may explain the reason for the conflicting conclusions regarding the influence of pregnancy on pulmonary tuberculosis, and certain suggestions are offered as bearing on future studies of the problem.

H. J. CORPER.

MULTIPLE PULMONARY ABSCESSSES FROM BLOOD INFECTION BY THE PROTEUS GROUP. M. J. KING and R. H. MORGAN, Am. Rev. Tuberc. **19**:182, 1929.

Recorded cases of human infection with *B. proteus* are infrequent. A case is presented in which positive blood cultures were obtained two hours after death. The micro-organisms were also cultured from lung abscesses and from pus in the frontal and maxillary sinuses. Repeated cultures of *B. proteus* were obtained from the sputum for several months before death. The organism was pathogenic for rabbits and guinea-pigs, and necrosis of the liver and heart muscles was produced in the experimental animals. A thermolabile toxin was produced in young broth cultures, which experimentally produced lesions comparable with those resulting from living micro-organisms.

H. J. CORPER.

HEMOPTYSIS IN TUBERCULOSIS FOLLOWED BY MASSIVE PULMONARY ATELECTASIS. JULIUS L. WILSON, Am. Rev. Tuberc. **19**:310, 1929.

Hemoptysis complicated by pulmonary atelectasis is extremely rare. The atelectasis may be logically attributed to the occlusion of a bronchus by a blood clot, but in no instance, apparently, has this been verified by recovery of the clot. The author reports a case in which a woman, aged 23, expectorated a bronchial cast composed of a blood clot. With this expectoration, the pulmonary atelectasis rapidly disappeared.

H. J. CORPER.

SOME SOURCES OF ACID-FAST BACILLI. STEPHEN J. MAHER, Am. Rev. Tuberc. **19**:376, 1929.

Acid-fast bacilli are forms of ordinary bacteria in which waxy capsules have developed to resist an unfavorable environment or forms resulting from the stimulation of acid-fast spores in an environment unfavorable to the full or ordinary evolution of these spores. Old tubercle bacilli, when suddenly transferred from an atmosphere saturated with their own ethers to one to which there is access of air, often grow wholly or partly free from their waxy capsules, and as rapidly as so-called pseudo tubercle bacilli. Acid-fast bacilli are to be found in, or can be cultivated from, several kinds of cancer. In internal cancer, they resemble the acid-fast colon bacilli, in uterine cancer the acid-fast bacilli and in cutaneous cancer either these same smegma bacilli or the coccal and ovoid acid-fast forms derivable from spore-bearing bacilli.

H. J. CORPER.

TUBERCULOSIS AMONG THE AMERICAN INDIANS. STEPHEN J. MAHER, *Am. Rev. Tuberc.* **19**:407, 1929.

The American Indians, even in the wild, suffered from tuberculosis, and the doctrine that tuberculosis is a curse that the white race has passed along to the other races of the world is false.

H. J. CORPER.

THE SICKLE-CELL PHENOMENON IN TUBERCULOSIS PATIENTS. VERA B. DOŁGOPOL and RICHARD H. STITT, *Am. Rev. Tuberc.* **19**:454, 1929.

The incidence of the sickle-cell phenomenon in seventy-seven tuberculous negro patients was found to be 5.2 per cent. The incidence of the sickle-cell phenomenon in 1,685 patients examined by different investigators was 6.5 per cent. With hereditary meniscocytosis, a greater prevalence of bizarre cells in the central portion of moist-chamber blood preparations is due to a greater asphyxiation of the erythrocytes in the center of the drop. Chronic anoxemia, caused by a disease or compression of the lung, is not an etiologic factor in the development of the meniscocytic anemia from hereditary meniscocytosis, nor can tuberculosis, syphilis and secondary anemia be regarded as etiologic factors.

H. J. CORPER.

THE TREND OF TUBERCULOSIS MORTALITY IN RURAL AND URBAN AREAS. EDGAR SYDENSTRICKER, *Am. Rev. Tuberc.* **19**:461, 1929.

The trend of the rural tuberculosis death rate was essentially identical with the urban tuberculosis death rate during the period from 1900 to 1915. Although the urban rate maintained itself with reference to the rural rate at a ratio of about 2 to 1, the proportionate decline was approximately the same in both populations. Immediately subsequent to the depression of the years 1914 and 1915 and in the influenza epidemic of 1918, a rise in mortality attributed to tuberculosis occurred; this was followed by a sharp drop in the rate of deaths from the disease in the years from 1919 to 1921. In these three years, the urban rate declined more rapidly than the rural rate. Since then, both rates have been declining somewhat more rapidly than in the period from 1900 to 1916. Without more detailed statistics, the following is offered: The net effect of the interplay of various factors on the tuberculosis death rate during the period from 1900 until the world war was approximately the same in urban and rural situations, but since then the forces favoring a decline have been somewhat more powerful in cities than in country districts.

H. J. CORPER.

EXPERIMENTS ON THE FILTRABILITY OF THE GRANULAR PHASE OF THE TUBERCLE BACILLUS. RALPH R. MELLON and ELIZABETH L. JOST, *Am. Rev. Tuberc.* **19**:483, 1929.

On injection of filtrates of tuberculous material from sixteen different sources, two animals of a total of thirty-seven yielded definitely positive results. Classic tuberculosis was reproduced, and the typical Koch bacillus recovered in pure culture. These positive results came only when the original material had been richly seeded with the granular form of the tubercle bacillus. Lesions which were possibly tuberculous also developed in two other guinea-pigs inoculated with filtrates from the same granular sources; these were not significant enough in the gross, however, to warrant further injection or culture. Evidence for the correctness of the filtration point of view can be based, in the beginning, at least, only on definitely positive results. In the absence of an isolatable tubercle bacillus from lesions that are histologically indistinguishable from known tuberculosis, one is not, with present knowledge of the life history of the tubercle bacillus, justified in drawing conclusions as to filtrability. Nor, on the other hand, is histologic evidence of tubercles in guinea-pigs of itself sufficient proof of filtrability. Such lesions have been caused by gram-negative paratyphoid-like micro-organisms. This was shown, not only by the isolation of the latter and

by their pathogenicity, but also by the failure of the histologically true tubercle to produce true tuberculosis when reinjected. The relation of this group of micro-organisms to lesions indistinguishable from the necrobiotic type of tubercle lesions in guinea-pigs must always be kept in mind.

H. J. CORPER.

A STUDY OF PULMONARY TUBERCULOSIS IN CHILDREN. A. LEVINSON, Am. Rev. Tuberc. **19**:499, 1929.

In ninety-nine of 119 cases of active tuberculosis, mainly in negro children, pulmonary involvement was found. Sixty-nine were cases of miliary tuberculosis; fifteen, acute tuberculous pneumonia, and fifteen, subacute or chronic pulmonary tuberculosis. The reactions to tuberculin were negative in all cases of miliary tuberculosis. In some cases, the tuberculin reactions, which were positive when the patient entered the hospital, became negative when repeated after the onset of a miliary process. The pulmonary involvement in both the acute and the subacute forms was rather extensive and was mainly caseo-ulcerative. The prognosis in all the acute cases was bad. Of the fifteen patients in whom the disease was chronic, eleven had died, one was living, but the disease was running a progressive course, two were lost track of and one was doing well.

H. J. CORPER.

THE RELATIONSHIP BETWEEN BLOOD SEDIMENTATION INDEX AND FIBRIN CONTENT IN TUBERCULOUS PATIENTS. ESTHER M. GREISHEIMER, CHARLOTTE C. VAN WINKLE and OLGA H. JOHNSON, Am. Rev. Tuberc. **19**:559, 1929.

A significant relationship was found between the fibrin content and the sedimentation index in the groups studied. In both sexes, a significant correlation existed between the fibrin content and the amount of sedimentation, as determined at intervals of from fifteen minutes to one hour.

H. J. CORPER.

THIRTY STRAINS OF GRAM-POSITIVE COCCI ISOLATED FROM GENITO-URINARY INFECTIONS. ASYA M. S. STADNICHENKO, J. Bact. **17**:303, 1929.

Thirty strains of gram-positive cocci isolated from thirty cases of genito-urinary infection were studied diagnostically. Following are the principal results: The most prevalent type of infection in this series was prostatitis. However, no correlation was established between this type of infection and the strain of cocci isolated in connection with it. Strains in this series had a tendency to ferment carbohydrates strongly. The following carbohydrates were fermented by almost all the strains: dextrose, sucrose, maltose, mannitol and glycerol. The ability of strains in this series to decompose urea was pronounced. On the whole, the white strains exhibited more variation in their cultural characteristics than the orange. The orange group proved to have a higher percentage of gelatin-liquefying, nitrate-reducing, milk-coagulating and urea-decomposing strains. In general, the orange strains were more active, and the infections in connection with which they were isolated were more severe.

AUTHOR'S SUMMARY.

THE EFFECT OF FILTRATES OF CERTAIN INTESTINAL MICROBES UPON BACTERIAL GROWTH. MARGARET F. UPTON, J. Bact. **17**:315, 1929.

*Bacillus coli* and *Micrococcus ovalis* are inhibited in bacterial filtrates of cultures of *B. coli*, *M. ovalis* and *B. bifidus* at a  $p_H$  value of 4.5 and 5. The inhibition appears to be due to some factor in addition to that caused by an increase in hydrogen ions. Acetic and formic acids show an effect similar to that shown by filtrates, which disappears as the acids tend to become neutralized. Lactic acid has a less inhibitory effect than the other acids studied. Under the same conditions, *B. coli*, *M. ovalis* and *B. bifidus* utilize lactose differently, giving different proportions of volatile and lactic acids. The question is discussed as to the connection between the presence of large amounts of volatile acids presumably produced by *B. bifidus* in the

intestine of the breast-fed infant and the inhibition of *M. ovalis* and *B. coli* in that locality. The prevalence of these last two organisms in the feces of the artificially fed infant, in which the reaction is less acid, would seem to correlate with the results obtained from experiments outlined in this paper.

## AUTHOR'S SUMMARY.

RELATIONSHIPS OF THE ENCAPSULATED BACILLI WITH REFERENCE TO BACT. AEROGENES. PHILIP R. EDWARDS, J. Bact. **17**:339, 1929.

The organisms that I have received from various sources labelled Friedländer bacilli cannot be distinguished from *Bacterium aerogenes* and the other members of the encapsulated group by action on milk or fermentative characters. Five cultures of *Bact. aerogenes* isolated from soil, water and milk have been found to be culturally, biochemically and serologically identical with type B of the Friedländer bacillus as described by Julianelle. Two cultures of *Bact. aerogenes* have been found serologically identical with a strain of the granuloma bacillus. *Bact. aerogenes* is so closely related to the other encapsulated forms that they should be classified in the same genus. No constant differences have been observed that could be used to separate the organisms into two or more species.

## AUTHOR'S SUMMARY.

DIFFERENTIATION OF *L. ACIDOPHILUS* FROM *L. BULGARICUS*. WALTER L. KULP, J. Bact. **17**:355, 1929.

The results of these experiments indicate that strains of typical *Lactobacillus acidophilus* can be separated from strains of representative *Lactobacillus bulgaricus* by the determination of their tolerance for indol or phenol. The slight tolerance of *L. bulgaricus* for indol and phenol in experiments in vitro may help to explain why *L. bulgaricus* is not able to survive passage through the digestive tract. Further studies are planned to determine the validity of this theory.

## AUTHOR'S SUMMARY.

OXIDATION-REDUCTION EQUILIBRIA IN BIOLOGIC SYSTEMS (POTENTIALS OF AEROBIC CULTURES OF *B. TYPHOSUS*). CALVIN B. COULTER and MOSES L. ISAACS, J. Exper. Med. **49**:711, 1929.

The reduction potentials of *Bacillus typhosus* in culture in bouillon that is given access at atmospheric oxygen show a negative drift which attains the values found in sterile bouillon deaerated with nitrogen: Eh  $-0.085$  to  $-0.095$  volt at  $p_H$  7.6. The potential reaches this level after from six to eight hours' incubation and is maintained at this point for several hours. A slow decline to more negative values is then observed and continues for at least forty-eight hours, at which time a potential of  $-0.145$  volt may be attained. The bacteria influence the potentials in the first period of their growth by exhaustion of oxygen from the culture, thus permitting the characteristic potential of the culture medium to become manifest, and do not contribute the substances responsible for the observed potentials. The decline in potential to values more negative than those of the culture medium occurs during the time that the rate of dying of the bacteria approaches and exceeds the rate of multiplication; it is suggested that dissolution of bacteria liberates reductive substances. Cultures in 0.5 per cent dextrose medium show a somewhat more negative potential after eighteen hours' growth than cultures in medium without dextrose. This may be due to the more rapid "turn-over" of the bacteria and the liberation of larger amounts of reductive material from the dissolution of larger numbers of bacteria. The potential of cultures through which oxygen is passed continuously does not show a negative drift at any time. This indicates that reductive substances of bacterial origin in the case, at least, of the typhoid bacillus do not influence the electrode potentials in the presence of oxygen and confirms the importance of bacterial respiration as the means for the removal of oxygen and the consequent establishment of characteristic reduction potentials in cultures.

## AUTHORS' SUMMARY.

RELATION OF VARICELLA TO HERPES ZOSTER. T. M. RIVERS and L. A. ELDRIDGE, JR., J. Exper. Med. **49**:899 and 907, 1929.

Varicella most frequently occurs in persons under 10 years of age, while zoster as a rule is observed in persons beyond that age. The number of cases of varicella exhibits a markedly constant seasonal variation. The variations in the prevalence of herpes zoster are not regular and do not parallel those of varicella. Experiments and clinical observations dealing with the identity of the viruses of varicella and herpes zoster are presented. The results indicate that the etiologic agents concerned with these two diseases are in the majority of instances not identical.

AUTHORS' SUMMARY.

ETIOLOGY OF OROYA FEVER. THE INSECT VECTORS OF CARRION'S DISEASE. HIDEYO NOGUCHI, RAYMOND C. SHANNON, EVELYN B. TILDEN and JOSEPH R. TYLER, J. Exper. Med. **49**:993, 1929.

The experimental observations described in this paper lead us to conclude that certain phlebotomi act as vectors of Oroya fever and verruca peruana. The phlebotomi that have been shown certainly to carry *Bartonella bacilliformis* are those of the species *Phlebotomus noguchii*. *Phlebotomus verrucorum* is also probably a vector, while *Phlebotomus peruvensis* in this respect remains doubtful.

AUTHORS' SUMMARY.

SOME NEW ASPECTS OF THE ETIOLOGY AND ENDEMIOLGY OF LEPROSY. ERNEST LINWOOD WALKER, J. Prev. Med. **3**:167, 1929.

The confusion and doubt surrounding the cultivation of the lepra bacterium are due largely to the pleomorphic and facultative acid-fast character of this organism. The acid-sensitive or partly acid-fast coccoid, diphtheroid and actinomycoid organisms that have been cultivated repeatedly from leprosy are different stages in its life cycle. Hansen's bacterium in leprosy lesions is probably the tissue stage. The organism belongs in the genus *Actinomyces*, as now constituted, and is most nearly related to the facultative acid-fast species, such as *Actinomyces asteroides* and *Actinomyces caprac*. The difficulty of cultivation of the lepra bacterium, the failure of experimental infections of man with leprosy material and many of the clinical and pathologic peculiarities of the disease appear to be due, in part, at least, to the fact that the majority of the lepra organisms in the tissues of lepers are dead. Proof of the identity of the actinomyces cultivable from leprosy and Hansen's bacterium, like proof of the etiologic relation of the latter to leprosy, depends on the experimental reproduction of the disease in animals. Notwithstanding the absence of such proof, the evidence in support of both relations is convincing.

The actinomyces of leprosy, like other pathogenic actinomycetes, is a soil organism probably of wide but irregular distribution, and is only a facultative parasite. Leprosy probably is primarily an infection from the soil, presumably through wounds; but contagion as a possible secondary mode of dissemination is not thereby excluded. The bearing of these conclusions on methods of control of leprosy is obvious. It may ultimately be found that protection from soil-infected wounds and proper cleansing and disinfection of contracted wounds are at least as important as the segregation and isolation of lepers.

AUTHOR'S SUMMARY.

BACTERIAL STUDY OF HEMOLYTIC STREPTOCOCCI FROM A MASSACHUSETTS OUTBREAK OF SEPTIC SORE THROAT IN 1928. ELLIOTT S. ROBINSON and EDITH A. BECKLER, J. Prev. Med. **3**:225, 1929.

From the bacteriologic study of the outbreak of septic sore throat in Lee, Mass., in July, 1928, it appears that the causative organism was *Streptococcus epidemicus*, the same etiologic agent found by others in previous outbreaks. This organism was found in the throats of a number of patients, in the aural discharge of some and in the blood of one. The milk-borne nature of the epidemic is shown by the

epidemiologic evidence presented by Lombard and by the finding of *S. epidemicus* in a cow that had been providing part of the milk consumed by the patients. The source of the cow's infection remains undetermined and probably undeterminable. By the usual criteria, *S. epidemicus* is of human, not bovine, origin, and it is reasonable, therefore, to suspect a human source. Although there was illness on the farm at a time when the cow might be supposed to have been infected, the epidemiologic evidence is not of itself sufficient to connect this illness with the infection of the cow, and there is not at present bacteriologic evidence to link the two. The isolation of *S. epidemicus* from the throats of patients is not difficult if one is familiar with the colony typical of this organism. Since there may be little hemolysis around the surface colony when grown on a moist medium, it may be overlooked; for the colony does not greatly resemble that of the more usual hemolytic streptococci. Culturally, the strains of *S. epidemicus* obtained during this epidemic appear identical with those isolated during previous outbreaks.

## AUTHORS' SUMMARY.

NEGATIVE RESULTS OBTAINED IN THE ATTEMPT TO RELATE TUBERCULOSIS SUSCEPTIBILITY OF RESISTANCE TO A PARTICULAR BLOOD GROUP. LELAND W. PARR, J. Prev. Med. 3:237, 1929.

The extensive literature dealing with the possible correlation of some particular blood group and susceptibility or resistance to tuberculosis is contradictory. The positive evidence indicates susceptibility in group A and resistance in group O. Entirely negative results are more numerous, however, and apparently more significant. The data here presented from 346 cases of clinical tuberculosis in Syria, in which tests for blood groups were made, fail to support the contention that there is any relation between susceptibility to tuberculosis and any one blood group. Similarly, no resistance to tuberculosis could be demonstrated for any one of the blood groups. In a series of tuberculin and blood-grouping tests, the 450 persons whose reactions to tuberculin were positive fell within the blood groups in the same proportions as the entire series of 944 persons. We conclude that all measures for the prevention and cure of tuberculosis should be applied to persons equally, irrespective of their blood groups, as persons of no one blood group appear to be significantly susceptible or particularly resistant to tuberculosis.

## AUTHOR'S SUMMARY.

A STUDY OF THE SIGNIFICANCE OF GEOGRAPHIC AND SEASONAL VARIATIONS IN THE INCIDENCE OF POLIOMYELITIS. W. LLOYD AYCOCK, J. Prev. Med. 3:245, 1929.

There is evidence that, in man, infection with the virus of poliomyelitis manifests itself in different ways: frank disease in relatively few and immunization without recognizable disease in the majority. Data presented in this paper indicate that these different reactions to infection with the virus may be due to variations in the physiology of the host, rather than to variations in the virus. Intracerebral inoculation of the virus in monkeys uniformly produces fatal poliomyelitis, and repeated intracutaneous inoculation of active virus produces immunity without symptoms of the disease, but neither of these methods reproduces an attack of the same degree of severity as that seen in man. It was found, however, that intranasal instillation of the virus reproduces poliomyelitis of nearly the same order of severity as that observed in man. The disease developed in only a portion of the animals following intranasal installation of the virus, and—what seemed to be more significant—in many of the animals a much milder form developed than that which practically always follows intracerebral inoculation. Furthermore, in one instance in which the animal showed no symptoms following intranasal inoculation, its blood serum in three separate tests was found to be capable of neutralizing the virus. From this, it appears that monkeys may possess a resistance to intranasal instillation of the virus not unlike that which man possesses to infection by natural means. It

may be possible, therefore, to gain further knowledge of this form of resistance to poliomyelitis (autarcesis) by testing the influence of artificial alterations in physiologic functions of the monkey on the results of intranasal instillation of the virus.

AUTHOR'S SUMMARY.

TUBERCULOUS ORIGIN OF IRIDOCYCLITIS. A. V. FRISCH and A. PILLAT, Arch. f. Ophth. **121**:504, 1929.

The authors believe that tubercle bacilli can produce every form of iridocyclitis from the simplest serous type to a panophthalmitis. The intracutaneous test for tuberculosis is the most sensitive and is harmless. On the basis of a positive intracutaneous tuberculin reaction and the general condition, together with an increased rate of sedimentation of the red corpuscles, which occurs frequently, a large number of cases of chronic recurring iridocyclitis can be considered as due to tubercle infection, in spite of the absence of typical tubercles. A large number of the cases of what was previously named "rheumatic" iridocyclitis belong to this group. The rate of sedimentation of the red blood corpuscles is increased in about 50 per cent of the cases of nodular iritis. The cases with a normal rate of sedimentation appear to proceed more favorably.

CHARLES WEISS.

PERISPLENITIS AND THE DISCOVERY OF SPIROCHETES IN CONGENITAL SYPHILIS. J. WATJEN and J. MUNZESHEIMER, Virchows Arch. f. path. Anat. **269**:325, 1928.

New and old perisplenitis occurs in more than one half of the cases of congenital syphilis and is often found accompanied by splenomegaly. This perisplenitis may be specific, for spirochetes were found in the splenic capsule and the perisplenic deposits. Spirochetes may wander into the capsule from the tissue immediately underneath it; also by way of the trabeculae, so that their deposition corresponds to the course of the connective tissue strands. Spirochetes may reach the peritoneal cavity from the splenic capsule, as demonstrated in six cases. That the reverse occurs, namely, perisplenitis from spirochetes within the peritoneal cavity, is not so probable.

STANLEY P. REIMANN.

REACTION OF THE VESSELS IN THE ISOLATED RABBIT'S EAR TO STREPTOCOCCI. A. P. ANOCHINA-IWANOWA, Ztschr. f. d. ges. exper. Med. **63**:792, 1928.

The author has previously reported experiments with streptococci and their toxins on vessels of the rabbit's ear isolated after the method of N. Krawkow. It was found that streptococcic (scarlet fever) toxin leads to a narrowing of the vessels in the isolated ear and later to edema of the tissue. These reactions are most pronounced if the temperature of transfusing fluid is from 37 to 39 C.

BALDUIN LUCKE.

LIBERATION OF TOXINS AND HEMOTOXINS FROM BACTERIA SUSPENDED IN BROTH AND IN SOLUTIONS OF DIFFERENT SALTS. N. FUJIOKA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**:466, 1928.

The experiments were made with the hemotoxin of cholera vibrios and the toxins of dysentery and of diphtheria bacilli. Suspensions of the bacteria were made in broth and in solutions of different salts, and the liberation of the toxin or hemotoxin was determined after short periods of extraction.

The bacterial suspensions in NaCl and KCl solutions liberated more toxin than similar suspensions in CaCl<sub>2</sub>, BrCl<sub>2</sub> or MgCl<sub>2</sub>. Diphtheria bacteria liberated more toxin in a two hour extraction period if suspended in NaCl solution than if suspended in broth; after longer periods, more toxin was liberated in the broth, owing to growth of the bacteria in the culture medium.

The author believes that the liberation of the toxin or hemotoxin depends on the influence of the different salts on the permeability of the bacterial cell.

R. C. AVERY.

LYMPHOGRANULOMA INGUINALE. SVEN HELLERSTRÖM, *Acta dermat.-venereol.*, 1929, suppl. 1.

It appears that inguinal lymphogranuloma can be traced back to the middle of the eighteenth century, and probably existed earlier. In Sweden, it was first described as a specific disease in 1927, but it is likely that it was observed by Ödmansson in 1887, and intracutaneous reactions indicate that it has existed there since about 1903.

A detailed account is given of forty-seven cases, two of them in women. In twenty-five cases, alterations were seen on the genitalia, the greater number being interpreted as primary. They consisted of erosion, superficial ulcer, nodule or papule, and urethritis; sometimes mixed chancre may have been concerned. The incubation from the probably infecting coitus to the appearance of adenitis is about one month. One "partner-case" as it is called, with isolated coitus, is described. In this, the periods of incubation were sixteen and twenty-one days. The city of infection in thirty-two cases was stated to have been Stockholm; in the remainder of the cases, the infection was acquired abroad. Erythema nodosum was observed in four cases, and inguinal lymphogranuloma is to be included among the infectious diseases which may be accompanied by erythema nodosum.

In every one of the forty-seven cases there was an undoubtedly positive reaction to Frei's intracutaneous test (extract of the pus in the affected lymph glands) for inguinal lymphogranuloma, carried out with seven different antigens, one of which had been obtained from Frei in Breslau. The antigens were tested and compared with each other, auto-antigen alone not being employed. In more than 60 per cent of the cases, Frei's reaction was carried out within a period of from one to three weeks to two months after the adenitis had been observed. The reaction was always positive. The persistence of cutaneous allergy, in one instance, was for twenty-four and a half years. It has not been possible to obtain any allergic reaction in healthy persons by intracutaneous injections of the antigen. If proper precautions are taken, the antigen remains active for more than a year. The Frei intracutaneous reaction appears to be specific.

Pathologic examinations and attempts to transfer the disease to animals resulted negatively. The anatomic picture in inguinal lymphogranuloma is not pathognomonic, and is, therefore, not sufficient for a diagnosis. Not all buboes are due to inguinal lymphogranuloma. In cases of inguinal adenitis, the etiology must be established by every possible means, before steps are taken to determine the histologic picture. Among the negative control-cases of Frei's reaction, were seventeen of *ulcus molle*, twelve with buboes.

The crossed antigen-tests between inguinal lymphogranuloma and climatic bubo, which resulted positively and which were verified by Fischer and Frei, appear to confirm the theory that inguinal lymphogranuloma and climatic buboes are identical. It has been impossible to determine any clinical or anatomic difference between the cases in which infections occurred in the tropics (climatic bubo) and those in which it occurred in Sweden.

There is described one case of extragenital localization of inguinal lymphogranuloma inguinale with positive intracutaneous reaction, which supports the theory that inguinal lymphogranuloma is a disease *sui generis*.

AUTHOR'S SUMMARY.

### Immunology

IMMUNIZATION AGAINST DIPHTHERIA WITH RAMON'S TOXOID. GEORGE F. DICK and GLADYS H. DICK, *J. A. M. A.* **92**:1901, 1929.

Ramon's toxoid was found a better immunizing agent than toxin-antitoxin.

BLOOD CALCIUM DISTRIBUTION IN ANAPHYLAXIS IN THE GUINEA-PIG. HERMAN BROWN and SUSAN GRIFFITH RAMSDALL, *J. Exper. Med.* **49**:705, 1929.

The results reported for total calcium and the membrane-diffusible fraction in the serum of the guinea-pig, taken at various intervals during anaphylactic shock,



confirm the observations of previous workers that the total calcium is essentially unchanged. There is, however, the further observation that the diffusible fraction is considerably increased over that found for the animal similarly treated but not manifesting characteristic symptoms.

AUTHORS' SUMMARY.

TRANSMISSION OF RESPIRATORY ANAPHYLAXIS (ASTHMA) FROM MOTHER TO OFFSPRING. BRET RATNER and HELEN LEE GRUEHL, *J. Exper. Med.* **49**: 833, 1929.

A further method is offered whereby sensitization in utero may be established. Respiratory anaphylaxis—induced in a pregnant guinea-pig by the inhalation of a dry antigenic dust—can thus be transmitted from mother to offspring. A guinea-pig thus sensitized in utero, when brought into contact for the first time with an anaphylactogenic dust to which the mother was sensitized, will manifest respiratory anaphylaxis. The transmission of this hypersensitiveness may be brought about passively through the transmission of sensitizing antibodies. A fetus may be actively sensitized in utero by a mother who has inhaled the antigenic dust and has not herself been sensitive at the time of birth. This state of hypersensitiveness may be transmitted in varying degrees of intensity, and when two or more offspring are born in the same litter, they may, in some instances, be sensitized to an equal degree and sometimes to different degrees. This state of hypersensitiveness can be transmitted through more than one litter. All animals cannot be made hypersensitive.

AUTHORS' SUMMARY.

A "SOLUBLE SPECIFIC SUBSTANCE" DERIVED FROM GUM ARABIC. MICHAEL HEIDELBERGER, OSWALD T. AVERY and WALTHER F. GOEBEL, *J. Exper. Med.* **49**:847, 1929.

By partial acid hydrolysis a specific carbohydrate may be isolated from gum arabic (acacia). This carbohydrate is comparable in its precipitating activity for type II and (type III) antipneumococcus serum with the bacterial soluble specific substances themselves. On hydrolysis this fraction yields galactose and two or more complex sugar acids, one of which appears to be a disaccharide acid comparable with those isolated from the specific polysaccharides of the type III pneumococcus and the type A Friedländer bacillus. The significance of these observations is discussed.

AUTHORS' SUMMARY.

SKIN REACTIONS IN RABBITS IMMUNIZED INTRAVENOUSLY WITH NON-HEMOLYTIC STREPTOCOCCIC. HOMER F. SWIFT and C. L. DERICK, *J. Exper. Med.* **49**:883, 1929.

Rabbits immunized intravenously with living culture or nucleoproteins of non-hemolytic streptococci react to subsequent intracutaneous inoculations with homologous streptococci with smaller and harder lesions than are shown by normal animals similarly inoculated; they do not show the general manifestations of hypersensitiveness such as are shown by animals the tissues of which were previously inoculated with the same cultures. A rabbit may react to intracutaneous inoculation with nonhemolytic streptococci in one of four ways, depending on whether it is normal, hypersensitive, immune or cachectic. Most normal animals show a secondary reaction about ten days after inoculation with suitable strains of non-hemolytic streptococci; hypersensitive, allergic, or hyperergic animals show much larger lesions than do normal ones with the corresponding doses of the same streptococci, and practically never show secondary reactions; immune animals show smaller and harder early lesions and usually do not have secondary reactions if they are fairly well immunized. Cachectic animals show soft and rapidly fading primary reactions and no secondary reactions.

AUTHORS' SUMMARY.

IMMUNOLOGIC REACTIONS WITH TOBACCO MOSAIC VIRUS. HELEN A. PURDY, *J. Exper. Med.* **49**:919, 1929.

Evidence is presented that a specific antibody to virus sap, lytic in nature, is present in the homologous antiserum from rabbits into which sap from tobacco plants affected with mosaic disease has been injected.

INTRADERMAL VERSUS SUBCUTANEOUS IMMUNIZATION OF MONKEYS AGAINST POLIOMYELITIS. F. W. STEWART and C. P. RHODES, *J. Exper. Med.* **49**: 959, 1929.

The introduction of considerable amounts of living, active poliomyelitis virus into the skin and subcutaneous tissue of monkeys protects the animals against intracerebral inoculations of similar virus material. The degree of protection conferred by intradermal is greater than that by subcutaneous injection. During intradermal and subcutaneous inoculations, no local or general pathologic signs were observed. The degree of protection produced by the immunization methods used is not absolute, since a percentage of the inoculated monkeys respond to intracerebral injections of highly potent virus. The serums of the animals inoculated intradermally or subcutaneously neutralized poliomyelitis virus *in vitro*, irrespective of the result of intracerebral inoculation, in all except one instance. The power of the serum of treated monkeys to neutralize virus *in vitro* is a more delicate test of immunity than is the intracerebral inoculation.

AUTHORS' SUMMARY.

YELLOW FEVER VIRUS. N. C. DAVIS and A. W. BURKE, *J. Exper. Med.* **49**:975 and 985, 1929.

While there are quantitative differences in virulence and minor differences in behavior, the African strain and the Brazilian strains of yellow fever virus studied in this work are immunologically the same.

ACQUIRED IMMUNITY IN AVIAN MALARIA: IMMUNITY TO SUPERINFECTION. WILLIAM H. TALIAFERRO and LUCY GRAVES TALIAFERRO, *J. Prev. Med.* **3**: 197, 1929.

Immunity to superinfection in bird malaria is evidenced by the fact that when large numbers of washed parasitized blood cells are introduced into the blood stream of a bird during the latent infection, they are quickly removed, whereas in normal birds they not only live, but increase rapidly in numbers. A quantitative study of the degree of immunity to superinfection—that is, the number of parasites that are removed, and the rate of removal by the bird during the latent infection—indicates that when the number of parasites injected into latent birds is approximately from 1 to 100 parasites per ten thousand red cells, the parasites are removed from the peripheral blood within twenty-four hours. If the number of parasites is increased from 100 to 400 per ten thousand red cells, they are removed within from forty-eight to seventy-six hours. The degree of immunity to superinfection may be less at the beginning of the latent infection than later. Removal of the parasites of birds during the latent infection takes place at all stages of the asexual cycle. It cannot be considered a phagocytosis of only the merozoites which are free in the serum. A high degree of immunity to superinfection was found as long as six hundred and fifty-six days after the primary inoculation of infected organisms.

AUTHORS' SUMMARY.

ACQUIRED IMMUNITY IN AVIAN MALARIA. THE ABSENCE OF PROTECTIVE ANTIBODIES IN IMMUNITY TO SUPERINFECTION. WILLIAM H. TALIAFERRO and LUCY GRAVES TALIAFERRO, *J. Prev. Med.* **3**:209, 1929.

The first report of this series demonstrated a highly effective parasitocidal mechanism in birds with a latent infection (immunity to superinfection). The present report demonstrates that this mechanism is not associated with a humoral antibody.

STREPTOCOCCUS TOXINS. H. VON HIRSZFELD, M. MAYZNER and F. PRZESMYCKI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **57**:414, 1928.

Forty strains of streptococci from scarlet fever, erysipelas and other sources were tested for toxins reactive with human skin. Positive results were obtained with almost all strains. Immunologic differences between the toxins were found in cross neutralization experiments with scarlet fever and erysipelas toxins and convalescent serums. In most cases the scarlet fever convalescent serums neutralized the toxin of scarlet fever strains but not the toxin of erysipelas strains. The erysipelas convalescent serums were less specific and usually neutralized the toxin of scarlet fever as well as the toxin of erysipelas strains.

R. C. AVERY.

INFLUENCE OF INJECTIONS OF SPLEEN EXTRACT ON IMMUNITY RESPONSE OF GUINEA-PIGS. HANS SCHLACK, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **57**:499, 1928.

The paper reports that the parenteral injection of spleen extract (freed from albumin and lipoids) increases the immunity response of guinea-pigs to smallpox vaccine, diphtheria bacilli and staphylococci. Negative results were obtained in similar experiments with pneumococci. The author believes that the action of the spleen extract can best be explained as due to a stimulation of the reticular endothelial apparatus.

R. C. AVERY.

## Tumors

THE PRODUCTION OF SARCOMAS BY THE IMPLANTATION OF EMBRYONIC PULP AND INACTIVATED CARCINOMATOUS PULP. VINCENZO BISCEGLIE, *Tumori* **3**:139, 1929.

No development of tumor was obtained by the simultaneous inoculation of rats with embryonal pulp and filtrates of carcinoma from rats. The pulp of carcinoma from rats is inactivated by exposure to chloroform (10 per cent) for three hours so completely that its inoculation remains constantly and completely negative. By simultaneous inoculation of inactivated pulp of carcinoma and embryonal pulp into twenty-five rats there was obtained in two animals a development of growths which on histologic examination proved to be sarcomas and which had given rise to metastases in the lungs and liver. One of these tumors was successfully transplanted. The sarcomatous tumors had probably taken their origin from embryonal connective tissue cells which had been exposed to the action of a tumor-producing agency in the inactivated carcinomatous pulp. The latter is probably a chemical product elaborated by cells the metabolism of which has been altered by various irritative agents.

W. OPHÜLS.

THE EPITHELIAL TUMORS OF THE BLADDER. ALFREDO FONTANA, *Tumori* **3**:185, 1929.

Fontana has studied eighteen specimens, fourteen obtained at autopsy and four at operation. At the pathologico-anatomic institute at Milano, 12 epithelial tumors of the bladder were found among 2,000 autopsies. He distinguishes benign and malignant papillomas and believes that the majority of carcinomas, especially the papillary ones, are derived from them. He also encountered typical primary adenocarcinomas of the bladder, associated with adenomatous proliferation of the prostate. He believes that in such persons there is a special proliferative activity of the vesicoprostatic glandular epithelium and that the physicochemical stimulus which produces it causes the malignant degeneration first in the bladder. The rare cases of malignant epithelioma of the bladder arise from areas of leukoplakia.

Contrary to common belief, Fontana found metastases in other organs in several cases of carcinoma of the bladder, among them twice in the suprarenals and twice in the bones. He believes that these tumors of the bladder develop in especially

predisposed organs as a result of various physicochemical stimuli. Other predisposing factors are stones, exstrophy and diverticula. W. OPHÜLS.

THE RELATION BETWEEN CARCINOMA AND LIPID METABOLISM. F. BURGHEIM, *Klin. Wchnschr.* 8:828, 1929.

In contrast with other diseases, the cholesterol in the blood of patients with carcinoma is increased after roentgen treatment. This variation disappears when the tumor is removed surgically. Malignant tissues contain large amounts of cholesterol, benign tissues, little or none. AUTHOR'S SUMMARY.

NEUROBLASTOMA OF THE SYMPATHETIC NERVE. C. BLUMENSAAT, *Virchows Arch. f. path. Anat.* 269:431, 1928.

Exceptionally, neuroblastoma of the sympathetic nerve may occur in adults. Pure sympathogoniomas have not been described in adults.

STANLEY P. REIMANN.

MIXED TUMORS OF THE LIVER. WERNER NISSELL, *Virchows Arch. f. path. Anat.* 269:446, 1928.

Mixed tumors of the liver are extremely rare. In the case reported, death resulted from hemorrhage due to rupture of the tumor. In addition to epithelial and connective tissue and parts histologically malignant, the tumor also contained cartilage and bone. The structure probably arose from epithelial and connective tissue elements in the liver anlage. The development of cartilage and bone may be explained by progressive metaplasia in Lubarsch's sense.

STANLEY P. REIMANN.

THE FREQUENCY OF PULMONARY CARCINOMA AND THE CAUSES OF ITS INCREASE. E. VON ZALKA, *Ztschr. f. Krebsforsch.* 26:130, 1928.

A study of the relative incidence of primary carcinoma of the lung in autopsy statistics from the hospital from 1894 to 1927 showed an increase in that time from 1.02 to 6.65 per cent of all cases of cancer. The rise occurred principally during the years after 1923. As regards etiology, while following influenza there are frequently changes in the lung of precancerous type, the importance of this infection as an agent is discounted by the frequent absence of a history of previous influenza. A second possible factor is that of exposure to war gases, also associated with altered epithelial relationships. A third conjectural factor is that of dietary insufficiency, since deficiency of vitamin A in experimental animals has been found to cause epithelial metaplasia. Of the possible factor of irritation by exhaust gases from internal combustion engines the writer makes only passing mention.

H. E. EGGERS.

THE RÔLE OF THE BLOOD VESSELS IN THE GENESIS OF TAR TUMORS. L. KREYBERG, *Ztschr. f. Krebsforsch.* 26:191, 1928.

The application of coal tar to the skin of white mice produces a marked local and lasting hyperemia, which appears to have a direct relationship to the ensuing epithelial hyperplasia. Effects which have been ascribed to the local alterations of nerve supply in these tumors may with equal warrant be ascribed to the vascular changes.

H. E. EGGERS.

THE NATURE AND THE CLINICAL VALUE OF THE CANCER REACTION OF ROFFO. H. HILAROWICZ and W. JANKOWSKA-HILAROWICZ, *Ztschr. f. Krebsforsch.* 26:214, 1928.

A study of the Roffo reaction for cancer — consisting of the addition of aqueous solution of neutral red to the serum to be tested, with a red coloration indicating

the presence of malignant disease—led to the conclusion that the altered reaction was due to the presence of increased globulin content in the serum. Clinical application did not show it to be of any great diagnostic value.

H. E. EGGERS.

HUMORAL AND CELLULAR GROWTH FACTORS OF CANCER CELLS. A. FISCHER, *Ztschr. f. Krebsforsch.* **26**:228, 1928.

Carcinoma cells are capable of obtaining nutritive material, as shown by continued and progressive growth in vitro, from serum and from inactivated embryonal extracts, differing in this respect from normal tissues. Also, carcinoma cells showed continued growth if they were in direct contact with fibroblasts, even if cultural conditions no longer permitted the growth of the latter.

H. E. EGGERS.

THE MEASUREMENT OF GROWTH OF CARCINOMA CELLS IN VITRO. A. FISCHER and H. LASER, *Ztschr. f. Krebsforsch.* **26**:235, 1928.

The residual energy and the inherent growth energy of carcinoma cells in Tyrode's solution were found to be somewhat less than those of normal tissues. If to the carcinomatous cells in vitro there were added normal tissues, the former showed an increased residual energy, which may be ascribed to the summation of the nutritive reserve of both tissues. Carcinoma cells grown in serum showed a considerable enhancement of growth if they were placed previously in contact with normal cells. By this contact they obtained an accessory principle, not nutritive in character, which acted as an accelerator of anabolism from the nutritive elements of the serum. This accessory factor is one of the important causes of unlimited proliferation in the organism. Carcinoma cells were found to be sensitive to embryonal extracts and to certain preparations of proteoses; with increased concentration of these there was an increase in the rate of growth, but with high concentrations the cells died rapidly.

H. E. EGGERS.

THE GROWTH OF CARCINOMA CELLS AND THE HYDROGEN ION CONCENTRATION OF THE MEDIUM. A. FISCHER, *Ztschr. f. Krebsforsch.* **26**:250, 1928.

Carcinoma cells were found to be very sensitive to variations of the hydrogen ion concentration of the medium. At a  $p_H$  of 5.9 growth no longer continued, although fibroblasts continued to grow for several days. On the other hand, cancer cells were less affected by increased alkalinity. The optimal hydrogen ion concentration for growth of malignant tumor cells is at least not more acid than that of normal tissues.

H. E. EGGERS.

THE PRACTICAL VALUE OF THE INTERFEROMETRIC METHODS IN THE DIAGNOSIS OF CANCER. F. P. TINOZZI, *Ztschr. f. Krebsforsch.* **26**:286, 1928.

The writer concludes that while the interferometric examination of blood serum offers so many complications, especially in the way of technical difficulties, it is of little practical value at present; improved and simplified methods may ultimately prove of importance in the diagnosis of malignancy.

H. E. EGGERS.

THE INFLUENCE OF VITAMIN UNBALANCE ON THE ORIGIN OF MALIGNANT TUMORS. R. ERDMANN and E. HAAGEN, *Ztschr. f. Krebsforsch.* **26**:333, 1928.

In a small percentage of rats (three of eighty-three animals surviving over four weeks) fed on a diet deficient in all vitamins except B and D, with the latter given in excess, there occurred spontaneous tumor development, which was shown by none of the control animals of similar descent on normal diets. The writers admit the possibility of congenital sensitiveness to vitamin unbalance. The latter condition they assume results in a lowering of cell unions, especially those of the reticulo-

endothelial system, by which the appearance of cell aggregates in reaction to external stimuli is favored, and these aggregates ultimately develop into tumors.

H. E. EGGERS.

NUCLEAR MEASUREMENTS IN TAR CANCERS OF WHITE MICE. W. EPANTSCHIN, *Ztschr. f. Krebsforsch.* **26**:439, 1928.

Following the continued application of coal tar to the skin of the white mouse, there is an increase in the size of the epithelial nuclei. The nuclei of the cells of tar cancers are characterized by marked polymorphism and increased size, comparable in these respects to those of cancers of the skin in men. In corresponding cancrioid tissues the polymorphism and increased size are present, but to a lesser degree.

H. E. EGGERS.

THE BIOLOGY OF CANCER CELLS IN VITRO. A. FISCHER, *Ztschr. f. Krebsforsch.* **26**:463, 1928.

Fischer's views of the biology of cancerous tissues, as revealed by tissue cultures, may be summarized as follows: Cancer cells are distinguished, even outside the living organism, by certain properties which they transmit to their offspring. Their enhanced growth is achieved by their ability to utilize as food-stuffs materials unsuited for normal cells. Also, they obtain a growth-stimulating factor by contact with normal cells. The differences in dynamic metabolism and in reactions to injury are revealed by their behavior in vitro. All differences are probably to be viewed as of quantitative rather than of qualitative character.

H. E. EGGERS.

ORGAN CHANGES IN MICE AFTER APPLICATION OF COAL TAR. W. BERGHOFF, *Ztschr. f. Krebsforsch.* **26**:468, 1928.

Following the long continued application of coal tar to the skin of white mice, three types of tissue change occur. Many animals show marked degenerative changes in the liver and kidneys; there is cellular proliferation, apparently of the reticulo-endothelial system, in the liver and spleen, and amyloid infiltration was seen especially in the spleen, more rarely in the liver and kidney. That these changes, especially the amyloid change, are not to be ascribed entirely to tumor action is shown by the fact that they occurred in animals without tumor. In either case their inception is probably to be ascribed to disturbance of the protein metabolism. All these changes were more pronounced in animals with developed tumors, which the writer interprets as indicating that tumors are most apt to form in those animals showing greatest organic injury. On the other hand, a series of mice fed with a diet high in iodized oil developed a high percentage of tumors, without showing amyloid infiltration. Evidently, the factors producing amyloidosis are not identical with those producing tumor. In general, Berghoff regards the degenerative changes as an indication of metabolic disorder which predisposes the animal to tumor formation, with the external irritation acting as the direct cause.

H. E. EGGERS.

### Medicolegal Pathology

RESISTANCE OF CRIMINALS AGAINST ACCIDENTAL AND SURGICAL TRAUMATISMS. C. GASPARINI, *Arch. di antrop. crim.* **48**:1, 1928.

An interesting discussion is based on several clinical observations illustrating a peculiar, extraordinary resistance of criminals against various kinds of physical and psychic traumatisms, such as severe injuries, operative procedures, dangerous infections, etc., a fact which Lombroso already had emphasized and designated as "disvulnerabilità." It is a characteristic somatic behavior exhibited by real criminals, and forms an important subject in the study of biology of criminals.

Similar observations can be made also among certain types of prostitutes, since prostitution can be regarded as a degenerative equivalent of delinquency. Such prostitutes show many somatic and psychic stigmas of degeneration, such as hypoalgesia, intellectual deficiency, impudence, aversion to work, etc. In spite of all possible and conceivable privations, exposures and hardships, the criminal remains unaffected. And in this respect there is a striking difference between the real, common criminal and the so-called political criminal. The mortality of the first group is low compared with that observed in short-termed prisoners. This surprising physical resistance is particularly evident toward abdominal wounds of any kind, ingestion of foreign bodies, etc., and in rapidity of recovery, so that Martini called the peritoneum of a criminal a "dog's peritoneum." Gasparini concludes that the biologically peculiar resistance of criminals against accidental and surgical traumatism forms one of the degenerative signs of delinquency.

E. L. MILOSLAVICH.

DISTRIBUTION OF THE BLOOD GROUPS AMONG THE CRIMINALS IN PIEMONTE.  
G. CANUTO, Arch. di antrop. crim. 48:687, 1928.

Among Piemontese criminals, an increase in the blood group B was observed with a corresponding decrease in groups A and AB; the A:B index is smaller than the racial biochemical index of the normal population of Piemonte. The preponderance of group B was found in persons who repeatedly committed one and the same delinquent act, as well as among those who had already been sentenced several times. In an analogous way, group B was often met with in criminals who were sentenced for various crimes. But a decided increase of group B was found in instances of homicide, robbery, violence, rape and rebellion, particularly if the perpetrators of these crimes were contrasted with other types of delinquents. There is an unmistakable correlation between group B and the presence of the somatic characteristics and external signs of degeneration that constitute the criminal type.

E. L. MILOSLAVICH.

PRACTICAL VALUE OF CRYSTALLIZATION OF HEMOGLOBIN FOR DIAGNOSIS OF BLOOD. F. NICOLETTI, Arch. di antrop. crim. 48:705, 1928.

Even prior to the time of the discovery of the precipitin test, crystallization of hemoglobin was intensively studied for medicolegal purposes in order to establish a reliable and specific method for differentiation of blood of various animal species. Falco was the first who studied it with the method of Amantea, using the highly hemolytic substance *Saponaria officinalis*; he believed that he was able to differentiate between human blood (adult as well as new-born) and that of other animals. The author now reports results of his investigations regarding human and animal blood, employing not only saponin, but also other chemicals, such as sodium fluoride and ammonia, particularly for fluid or clotted blood. From the results obtained, he concludes that only certain animals (guinea-pig, mouse, rat, squirrel) possess a constant and characteristic type of hemoglobin crystallization which allows one not only to diagnose the species in question, but also to differentiate between human blood and that of other animals. Some animals (dog, cat, hog, horse, rabbit, chicken, man, etc.), however, do not show any specific morphologic peculiarities that could be used to determine successfully the respective species. In some animals (guinea-pig, mouse, horse, rabbit), the blood pigment crystallizes only while in the state of oxyhemoglobin; in other species (cat, man, etc.) exclusively as reduced hemoglobin, while the blood pigment of such animals as dog, chicken and hog produces crystals from reduced hemoglobin, as well as from oxyhemoglobin. From all the methods described to date to obtain crystallization of hemoglobin, the best one is the saponin method of Amantea. Such a crystallization is also readily achieved if one uses tungstate, molybdate, phosphate and particularly sodium sulphate. The blood pigment of a given species generally needs for crystallization a definite period of time, which differs from that required by the blood pigment of another species (for instance, that of a guinea-pig or a

mouse will crystallize in from a few minutes to from one to four hours, that of a hog in from eighteen to twenty hours). This phenomenon is independent of any physical or chemical influences. The individual crystals, observed under a polarizing microscope, do not present any optic properties that would enable one positively to differentiate between the hemoglobin of various animal species. The following facts would, with great probability, permit the diagnosis of human blood: (1) the presence of crystals of reduced hemoglobin; (2) occurrence of crystals in exclusively tabular form (rectangular tables); (3) a time period for the crystallization of not less than twenty-four hours; (4) after a few days a tint of violet in the hemoglobin crystals (not noticeable in other species), and (5) a relatively short durability of the specimens prepared.

E. L. MILOSLAVICH.

MENTAL AND PHYSICAL COMPETENCY FOLLOWING A BULLET WOUND OF THE HEAD. W. WEIMANN, Arch. f. Kriminol. 82:178, 1928.

A man noticed no ill effects after shooting himself in the right temple. He felt the bullet pass out of the left temple. He lay in bed, but was completely oriented, and at a judicial hearing the next day made a clear statement. The wound healed after brain tissue and particles of bone had escaped and trephining had been done for abscesses that developed. It was assumed that the anterior horns of the lateral ventricles had not been opened and that certain so-called "blind" regions of the brain were the only parts injured.

E. R. LECOUNT.

SUBENDOCARDIAL HEMORRHAGE AND ITS SIGNIFICANCE. J. GERINGER, Beitr. z. gerichtl. Med. 8:105, 1928.

Subendocardial hemorrhages were found more frequently in bodies examined because the deaths were definitely subject to medicolegal inquiry than in those examined simply because death was not expected and health regulations in Vienna required their examination. In the first group there were only twenty bodies with subendocardial hemorrhages in 1,740 (1.2 per cent) examined post mortem; in the second group, the hemorrhages were in eighty-two of 707 bodies (11.5 per cent). Their cause, location, size and relation to the bundle of His conduction bands are reviewed with the literature and many tables of statistics. It was found that they are more frequent with death from hemorrhage and especially internal hemorrhage. Injuries of the head, particularly when there is an accompanying compression of the brain, metallic poisons, convulsions, apoplexy and tumors of the brain are other important causes. The hemorrhages as a rule are under the lining of the septal portion of the left ventricle; in only three hearts were they in the right ventricle.

That they are a consequence of postmortem rigor in the heart muscle, as has been claimed by Sury, is denied by Geringer, who, however, admits that they may be agonal or pre-agonal. They occur more with death from slow bleeding than with death taking place quickly from the loss of a large amount of blood. As a rule, there was but little blood in the heart chambers. The subendocardial hemorrhages were not related in any way to arteriosclerosis or to age. In this report there is practically no reference to the influence that fibrillary contractions at the time of death or failure of all portions of the myocardium to cease contractions at the same time may have in causing these hemorrhages, although, as already stated, Geringer does suggest that they may be agonal.

E. R. LECOUNT.

ANEURYSMS OF THE CEREBRAL ARTERIES. K. SZEKELY, Beitr. z. gerichtl. Med. 8:162, 1928.

Medicolegal postmortem examinations sometimes disclose extensive interleptomeningeal hemorrhage from ruptured aneurysms of the cerebral arteries as the explanation for sudden death. Because vomiting is often one of the symptoms of such hemorrhages, poisoning is suspected. In 11,500 necropsies at Vienna in the



Institute for Legal Medicine, there were 157 such deaths, or 1.4 per cent, and during the same period 348 from intracerebral apoplexy. A belief has long prevailed that the middle cerebral arteries are the seat of these aneurysms more than other arteries of the brain, but Szekely found the hemorrhages were far more frequently from aneurysms of the anterior communicating artery (table).

Another surprise in his summary is the greater number of such hemorrhages in women, the ratio of females to males being 65:35. In women, the aneurysms were mainly of the carotid system; in men, of the vertebral arteries and the vessels formed by them. Three fourths of all the 157 hemorrhages occurred in persons

*Distribution of Aneurysms of Large Intracranial Arteries*

	Per Cent		Per Cent
Anterior communicating .....	32.0	Left internal carotid.....	3.7
Right middle cerebral.....	15.0	Right internal carotid.....	2.5
Left middle cerebral.....	12.3	Left posterior cerebral.....	2.5
Basilar .....	9.0	Right communicating.....	1.5
Right anterior cerebral.....	6.2	Right vertebral.....	1.5
Left vertebral .....	5.7	Right posterior cerebral.....	0.6
Left anterior cerebral.....	5.5	Left communicating.....	0.6
Inferior anterior cerebellar.....		0.6	

aged 35 or older. The persons were not all adults, four being 20 years of age or less, the youngest of whom was aged 8. The aneurysms were nearly all small, only four being hazelnut or cherry sized. They were commonly at the site of branching; eight where the vertebral arteries unite to form the basilar artery. Syphilis is said to have caused a small number, but many more were from atherosclerosis and high blood pressure. When death was not immediate, the symptoms, in addition to the vomiting referred to, were dizziness, headaches, etc., rather than focal symptoms.

E. R. LECOUNT.

CATALEPTIC RIGOR MORTIS LEADING TO DETECTION OF MURDER. W. H. SCHULTZE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:13, 1929.

The occurrence of rigor mortis immediately after death is rather rare, and only a few thoroughly investigated cases have been accepted. Some pathologists with an experience of many years have never observed this condition. The case reported by Schultze was that of a man shot through the head from right to left as he was sitting on a stool before a writing table. The body and the room and its other contents were taken in charge by the police at once, and when Schultze came he found the stool up-turned and the body prone with the right hand and arm underneath and the left arm bent, the thorax and abdomen not touching the floor. The back was a little bowed and the legs slightly bent. There was a pen in the right hand and a piece of paper in the left, both grasped firmly. It was concluded that rigor came on immediately when he was shot. It was present in all parts of the body.

The son-in-law at first denied having done the shooting, and was confounded when the body was turned over and writing materials found so tightly held; evidently he had not known that they were there. Subsequently, he confessed.

E. R. LECOUNT.

HELP BY THE MOTHER DURING LABOR, CAUSING DEATH OF THE CHILD. W. H. SCHULTZE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:21, 1929.

Difficulty in explaining the injuries and death of a newly born child finally resulted in tracing them to an arm presentation and self-delivery by the unwed mother when she was alone. The swollen left hand, the direction and location of

abrasions and nail scratches corroborated the story told by the mother. A fracture of the cranium and an injury of the brain occurred by pressure of the head in the birth canal, when the child was born "conduplicato corpore." The self-aid was successful because the woman was a multipara and labor several weeks too early; the weight of the child was only 1,700 Gm. The child was born alive and lived about two hours. For a time, the mother was suspected of infanticide.

E. R. LE COUNT.

CHANGES OF RENAL BLOOD VESSELS IN EXPERIMENTAL POISONING WITH BICHLORIDE OF MERCURY. B. A. PHOTAKIS and E. NIKOLAIDES, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:28, 1929.

Swelling, shrinkage and necrosis of the endothelium of both the intertubular and glomerular capillaries, with hemorrhage and subsequent collapse and contraction of the malpighian bodies, were found in dogs given from 0.005 to 0.01 Gm. of bichloride of mercury per kilogram intravenously. The investigators maintain that the changes are not so exclusively in the epithelium as has been claimed, and that the term bichloride of mercury "nephrosis" is not suitable.

E. R. LE COUNT.

PROOF OF ARSENIC POISONING AFTER CREMATION. M. H. REMUND, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:33, 1929.

Five years after the death of a man and the cremation of his body, suspicions of poisoning were aroused by attempts to blackmail the widow. From the ashes, which had been preserved in an urn, 47.2 mg. of arsenic was recovered. Of this, about 40 Gm. was accepted as belonging to the Paris green that the widow had used; the remainder was possibly derived from various other sources, such as the hardware of the casket, the urn, arsenic normally present in the body, etc. On this basis, it was concluded that the amount of arsenic in the body before cremation must have been at least 0.4 Gm. The lethal dose is from 0.1 to 0.2 Gm. Probably, a large factor in deciding as to the arsenic poisoning was the use of coke from the gas works in the crematory, such fuel being free from arsenic. Moreover, no other fuel had ever been used there.

Experiments were made with other bodies of persons dying from natural causes, one that of a person who had died from acute arsenic poisoning, and with bodies of lower animals. One interesting experiment was placing organs from an animal poisoned with arsenic under bones from a normal animal and finding that, by sublimation, the bones became heavily impregnated with arsenic. This is important because of its bearing on the common belief that large amounts of arsenic accumulate in the bones during life.

E. R. LE COUNT.

SUICIDE BY STRANGULATION. A. M. MARX, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:104, 1929.

The opinion is generally held that it is impossible for a person to throttle or strangle himself so that death results. One reason for the holding of this view is that postmortem examinations alone fail to decide whether death is from murder or suicide. Marx reports two cases in which the circumstances left little doubt that self-strangulation had caused death. One concerned an insane mother who, after beating a daughter unconscious, strangled herself in bed by pulling a silk cord tight. The knot of the cord was on the left side of the neck, and the daughter was crippled from infancy and moved only in a wheel chair. In the second case, an insulated electric wire was wound about the neck nine or ten times, and where each coil lay against the loop at the end, the insulation was abraded because it had been pulled so tightly. The body was found in a farm field six weeks after suicide. His hand writing was identified; the content was a tale of domestic trouble.

E. R. LE COUNT.

IMPORTANCE OF THE DISTRIBUTION OF ARSENIC IN THE BODY. S. SCHÖNBERG, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:111, 1929.

Not only the amount of arsenic found in different parts of the body is important, but also its location is of value in determining how it was administered. Following a single, but not fatal, oral dose in rabbits, the rabbits being killed at different times, the arsenic disappeared from the content of the stomach and bowel first; reached its peak in the liver in the thirty-fourth hour; was absent from the kidneys but present in the brain in considerable amounts on the seventh day, and at this time was found in the skin and hair in  $\frac{1}{8}$  of the amount given and in the liver in only  $\frac{1}{100}$ .

In two rabbits receiving a single dose intravenously and killed, one four and the other eighteen hours later, there were traces in the wall of the stomach and bowel, but none in their content. The distribution and amounts in those killed some time after the last of a number of doses were similar to what was found in those killed some time after a single dose. When killed earlier after the last one of a number of administrations, the quantity in the hide, as well as in the stomach, bowel and liver, definitely indicated multiple doses. Conditions in, and indications from, the bones were similar to those in and from the skin and hair. Arsenic is present in the brain for relatively long periods after a single dose.

E. R. LE COUNT.

SPECTROGRAPHIC EXAMINATION OF BULLETS. W. SCHWARZACHER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:226, 1929.

French investigators made a spectroscopic study of the composition of the projectiles of the "Big Bertha" used to bombard Paris during the World's War. In a few cases information gained by this method concerning the various metals of the missiles of revolvers and other small weapons has been of great use in prosecuting crime. Spectrum analysis of the metallic jackets of seven bullets of different calibers and of their lead cores, and also of four unmantled bullets, was made. Three of the naked bullets or cores contained copper and iron, or iron alone, in addition to lead; only one was pure lead. The mantles, however, had a much more varied composition, some containing as many as eight elements, including such rare metals as scandium and vanadium and zirconium. Cobalt, aluminium and silver were also found.

The weapons from some firms, although taking cartridges of different calibers, had mantles for the bullets with a similar group of metals in them. But this was not true for the bullets of other firms making guns of a particular kind. By dissolving the metals in nitric acid and using solutions of from 0.1 to 0.0001 per cent, some indication was obtained of the quantity of each metal present.

E. R. LE COUNT.

DEMONSTRATION OF FAT AND AIR EMBOLISM. OTTO SCHMIDT, *Deutsche Ztschr. f. d. ges. ger. gerichtl. Med.* **13**:231, 1929.

Two deaths are reported, one from fat embolism following a broken leg, the other from air embolism due to the use of a rubber syringe to bring on an abortion. In each body, the foramen ovale was patent, and the emboli were easily and promptly found grossly in the vessels of the choroid plexus. Since air readily enters veins torn across when the skull cap is removed, or both veins and arteries of the brain when such vessels are cut in removing the brain, the suggestion is made that possibly one or both procedures should be carried out under water.

E. R. LE COUNT.

DELAYED DEATH AFTER PENETRATING WOUNDS OF THE HEART. K. MEIXNER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:250, 1929.

Wounds penetrating the right auricle of the heart are not so abruptly fatal as are those penetrating other parts of the heart. But when the right auricle is torn

or perforated from in front, some of the large blood vessels are generally injured and death comes on quickly. There is a place between the mouths of the superior and inferior vena cava where the sinus of the right ventricle may be perforated and death may not occur so promptly. Meixner describes two such wounds, one, a laceration from blunt force, reported by Geringer (*Beitr. z. gerichtl. Med.* **3**:1, 1919); the other, a stab wound and his own observation. A third and much more remarkable case is that of a man who lived twenty-five days after he had shot himself, the bullet passing into the right ventricle, through the interventricular septum, through the base of the front mitral leaflet and into the wall of the left auricle, where it lodged. Infection of the wound set in and death was from pyemia and metastatic abscesses of the brain, rather than from wounds of the heart.

E. R. LE COUNT.

THE INFLUENCE OF HYDROCYANIC GAS ON THE COLOR OF LIVORES. W. LAVES, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:261, 1929.

Among the several theories for the bright red patches in the skin after death from prussic acid and its compounds, none is altogether satisfactory. The most acceptable assumes that they are a result of postmortem diffusion of the volatile acid in its gaseous state. Many experiments were made by Laves, all supporting such a view. The wide-spread belief that such pink or scarlet livores are a common effect of poisoning by HCN is not in accord with the facts. At the Institute of Legal Medicine in Graz during twenty years, twelve deaths, it was decided, resulted from HCN. One body had bright red patches in the skin with the blood a similar color. Two others had such red livores, but the blood was dark. No such changes were observed in the other bodies. Laves took pieces of skin containing the usual grayish-purple livores and after covering all but the external surface of some and the deeper surface of others with paraffin found they became bright red when exposed to HCN.

Other experiments were made with bodies of persons dead from natural causes and with conditions arranged to ascertain the effect of temperature and moisture on the rate of diffusion of HCN. It was learned that this gas diffuses about twice as fast as  $O_2$ , that some of the red color of cadaveric spots is due to  $O_2$  entering the body from without and that diffusion of gases from without into the body is greatly aided by the moisture which collects on the skin when bodies are kept in cold, damp places. A diffusion of HCN outward toward the surface takes place when sodium cyanide, for example, is swallowed and when the gas kills persons who inhale it after entering buildings or the holds of ships too soon after its use as a vermifuge or a rat poison. The immediate death which it causes is also in agreement with postmortem formation of whatever color changes are made by this powerful swift poison.

E. R. LE COUNT.

NEW INTERPRETATIONS FROM POSTMORTEM EXAMINATIONS. RAESTRUB, *Deutsche Arch. f. d. ges. gerichtl. Med.* **13**:291, 1929.

Of all the many varieties of objective evidence useful in medicolegal investigations that furnished by postmortem examinations is by far the most valuable. Raestrub believes that there is a marked and increasing tendency to overlook this, and that one of the many forces now responsible for belittling the significance of such evidence is incompetency of prosecuting officials and police engaged in criminal work. He deplores the accord between these officials and the effect that premature announcements resulting from their co-operation have on judicial proceedings. Another factor is the disposition to omit postmortem examinations and from such information as the police furnish and merely a cursory inspection of the outside of the body, to decide what caused death.

To illustrate his disapproval of this trend of affairs Raestrub, working under Kockel in the Institute of Legal Medicine, refers to several experiences which they had there at Leipzig. One was a plea of self defence made by a man who claimed

that the stab wound of the neck in his antagonist, who died, was incidental to a scuffle during which he simply tried to brandish the weapon and to use only the flat side of the blade. It was necessary to insist that a postmortem examination should be made. When this was made, a second deep stab wound into the thorax through the sternum and penetrating the aorta was found, a wound which must have been made with great force. Death was not, as had been claimed, from bleeding from the wound of the neck, but was internal and from the wounded aorta.

Another death thought to be from hemorrhage from radial blood vessels cut in the wrists was found by the postmortem examination to be from suffocation; the throat was plugged by a gag placed there by the woman when she tried unsuccessfully to kill herself; the important radial vessels were intact.

Two other murders were sex crimes. Both bodies were found in the same locality, one that of a girl, aged 13; the other, that of a boy of the same age. Thorough examination of the body of the girl, who was killed first, and of her clothes, left no other possible conclusion except that she was first assaulted and then drowned, and a report to that effect was given the authorities. A few days later, to the great astonishment of Raestrub and his colleagues, a statement appeared in the newspapers, that death from violence was improbable and that the injuries were from epileptic fits. This announcement came from an expert consulted by the police, and from one who, moreover, was not present at the examination of the body. Two years later, the boy was killed and again the newspapers opposed the conclusions of those at the Institute of Legal Medicine, who were forced to believe that both murders were probably committed by the same person.

E. R. LE COUNT.

RUPTURE OF THE UTERUS. M. KRÜGER-FRANKE, München. med. Wchnschr. **75**: 132, 1928.

The mortality from rupture of the uterus is from 30 to 60 per cent. The author had six recoveries after hysterectomy in seven cases. He mentions as causes scars from operations involving the body of the uterus, abortion, puerperal fever, tears from labor, administration of preparations of hypophysis and defective training of physicians for obstetric work. Tears lengthwise in the cervix and tears in Bandl's constriction ring are the common locations of the lacerations. The patients are excited, have a redness of the face, suffer from repeated pains due to uterine contractions and have a tender lower uterine segment.

E. R. LE COUNT.

### Technical

THE DIAGNOSTIC VALUE OF A COLORIMETER FOR THE MELTZER-LYON TEST. EDWARD HOLLANDER, Am. J. M. Sc. **177**:377, 1929.

A colorimeter was used in 100 consecutive cases of cholelithiasis for the determination of the volume and color intensity of the dark bile obtained by duodenobiliary drainage, which is assumed to be derived from the gallbladder and which is commonly known as "B" bile. The bile was also examined microscopically. Gross disease of the gallbladder was present when the following observations were made: (1) no "B" bile; (2) from  $\frac{1}{3}$  to  $\frac{2}{3}$  of the normal amount of "B" bile without cholesterol crystals; (3) from  $\frac{1}{3}$  to  $\frac{2}{3}$  of the normal amount of "B" bile with agminated cholesterol crystals. When the amount of "B" bile was normal, the gallbladder at operation was practically normal in size and shape and was functioning through an open cystic duct. When agminated cholesterol crystals precipitated on particles of bile-stained debris were present in these cases, cholesterosis of the gallbladder with or without stones was found. In 4 per cent of the cases of cholelithiasis in which calculi were present in a normal-sized gallbladder, the amount of "B" bile was normal and agminated cholesterol crystals were absent.

PEARL M. ZEEK.

THE VOLUME AND HEMOGLOBIN CONTENT OF THE RED BLOOD CORPUSCLE.  
MAXWELL M. WINTROBE, Am. J. M. Sc. **117**:513, 1929.

Simple methods are described for the calculation of the volume and hemoglobin content of the red blood corpuscle. Healthy young adult cells vary from 70 to 98 cubic microns in diameter and contain 28.7 by  $10^{-12}$  Gm. of hemoglobin, the latter occupying about 33.3 per cent of the entire volume of the cell.

PEARL M. ZEEK.

SUGGESTIONS FOR STAINING TUMORS OF SPONGIOBLASTIC ORIGIN. NATHAN  
CHANDLER FOOT, Am. J. Path. **5**:215, 1929.

A method is described whereby the Globus-Hortega technic is combined with the hematoxylin-van Gieson stain, so that a polychrome picture results. It is believed that this gives slides that are more readily interpreted and have a greater similarity to routine sections than is the case with those impregnated with silver alone. They are also better suited to photomicrography.

AUTHOR'S SUMMARY.

METHODS FOR GROWING BRUCELLA ORGANISMS FROM FECES IN UNDULANT  
FEVER. H. L. AMOSS and MARY A. POSTON, J. A. M. A. **93**:170 (July 20)  
1929.

About 1 Gm. of fresh feces was mixed in 50 cc. of sterile isotonic salt solution and shaken for a few minutes to insure thorough suspension. The suspension was filtered through four layers of number 1 hospital gauze to remove gross particles and centrifugated at half speed for three minutes to throw down other particles and larger bacteria. To the supernatant suspension, a sufficient amount of immune serum was added to make the total dilution 1:100, and after being shaken the mixture was placed in a water bath at 37 C. for two hours. The suspension was centrifugated at half speed for five minutes and the supernatant fluid discarded.

The precipitate was resuspended in isotonic salt solution, stirred and centrifugated at the same speed again. The supernatant fluid was again discarded and the procedure repeated twice. Finally the precipitate was spread with a bent glass rod on eosin-methylene blue plates, some of which were incubated at 37 C. aerobically and others in an anaerobic jar containing 10 per cent carbon dioxide.

Large clear colonies appeared after ninety-six hours. These were fished and the organism identified in the usual manner.

By this method a *Brucella* strain corresponding immunologically to Hygienic Laboratory strain 428 has been cultivated thirty-six times from the stools of a patient suffering from *Brucella* peritonitis and oophoritis. *Brucella abortus* (porcine) has been isolated from the stools of another patient in the sixteenth month of his infection.

BLOOD AND BONE-MARROW CELLS OF THE DOMESTIC FOWL. CLAUDE E.  
FORKNER, J. Exper. Med. **50**:121, 1929.

A simple, direct method of counting leukocytes of the fowl is described. Twenty-nine complete, morphologic studies of the blood of eleven domestic fowls are recorded. The characteristics of the cells found in the blood and bone-marrow are described in detail, and their relative numbers reported. The supravitral technic, in which neutral red and Janus green are used, enables one to separate and classify accurately the confusing cells of the blood and bone-marrow. These studies provide a basis for future experimental studies on the blood and bone marrow cells of the fowl.

AUTHOR'S SUMMARY.

HISTO-TOPOCHEMIC EXAMINATION OF DISEASED ORGANS BY INCINERATION OF SECTIONS (SCHNITTVERASCHUNG). O. SCHULTZ-BRAUNS, *Virchows Arch. f. path. Anat.* **273**:1, 1929.

For years, attempts have been made in botany and in human histology to define chemical substances in the tissue itself. For technical reasons, the results have not been good. The usual methods of fixation alter most of the tissue substances, and most methods of staining have not the value of chemical reactions.

Frozen sections are made from unfixed material of any organ. The sections are kept at a uniform thickness of 15 mikrons for the purpose of comparison. Many tissues can be cut much thinner. Such thinner sections are treated as ordinary tissue slides for comparison and for exact localization. The frozen sections must be prevented from melting and from any contact with water. This is effected by keeping the microtome knife and the instruments with which the section comes into touch below zero. A second freezing chamber cools the microtome knife (from above). A frozen drop of water near the handle of the knife indicates the necessary low temperature. The sections are transferred to dry glass slides, which must be clean. The incineration is done in a quartz furnace through which moist oxygen passes. Such slides, when examined in reflected light show the ash substances exactly in their original location. In the beginning of the incineration, carbon forms; later on, at higher temperatures, the carbon is burned to carbon dioxide. During these two processes, minute details of the tissue structure become distinct because they have different resistance to the high temperatures (isotropic and anisotropic substance of muscle, nuclei of epithelial cells, etc.). Between 100 and 150 degrees, the connective tissue, especially when hyalinized, becomes opaque and seemingly doubly refractive; this is due to an increased amount of air in it. When the heating is too rapid, bubbles of tarlike substances may cause artefacts. The furnace contains a thermometer, and the heating is carefully regulated by an electric resistance.

In many instances, the amount and distribution of the ashes in the tissue are surprising. In blood vessels, much more of ashes is found than would correspond to the lime substances as stained with hematoxylin. The aorta of the new-born infant contains a little more of ashes than that of a one year old child. Increase of ashes and changes in their distribution are found in cartilage which looks normal in the usual slide. Fresh caseation contains little ash substance; old caseation much. Normal lung tissue of young persons is nearly ash-free, especially in tuberculous people. But the thin and normal-looking alveolar walls of a man aged 80 were full of ashes. It was the same with an atelectatic apical scar. Ash changes in epithelium are small. Some of the ashes are situated in living cells, but probably these cells are impaired in their metabolism (cartilage surrounded by inflammatory foci, inflamed gallbladder, heart muscle fibers near scars). The chemical differentiation of the ashes in the incinerated slide naturally is difficult, in view of the extremely small amounts of substances concerned. Brown color of ashes is due to iron contents; such ashes are mainly found in organs with stasis. For potassium, McCallum's method can be used. The hematoxylin reaction is no direct indicator for calcium; it is positive only in the presence of iron. The calcium salts can be recognized in an indirect way by their poor solubility. After a slide is washed in distilled water for ten minutes, only the calcium salts remain. Some of the ashes are bluish. This is due only to quantity; fine layers of ash substance appear blue no matter what they consist of. There are great new possibilities for this method.

ALFRED PLAUT.

# Society Transactions

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## PHILADELPHIA PATHOLOGICAL SOCIETY

*Annual Conversational Lecture, April 11, 1929*

J. HAROLD AUSTIN, *Presiding*

SOME CONTRIBUTIONS OF TISSUE CULTURE TO PATHOLOGY. WARREN H. LEWIS.

The literature on the contributions of tissue culture to pathology is so extensive and varied that one can cover but a small part of it in a single lecture. There are already several hundred articles dealing with tumors, tuberculosis, viruses, immunity, cytotoxins, bacteria, phagocytosis, allergy and the effects of radium, x-rays and various chemicals and toxins on cells.

### ALLERGY

The allergic reaction in tuberculosis had generally been regarded as the result of a reaction between antigen and antibody, but uncertainty existed as to whether it was cellular or humoral until Mrs. Lewis and Dr. Rich (1928) added to cultures of spleens and of washed white blood cells from normal and from allergic guinea-pigs, measured amounts of tuberculin. This showed in the clearest manner that the cells from allergic animals are more sensitive to the effects of tuberculin than are those from normal animals. They are killed by amounts of tuberculin in which normal cells grow freely. This sensitiveness of the washed cells of allergic animals was exhibited regardless of whether they were exposed to tuberculin in plasma of normal or of allergic animals. Tuberculin in allergic plasma had no more effect on normal cells than had tuberculin in normal plasma. They concluded that cellular injury and necrosis associated with allergy in tuberculosis result from a change in the individual fixed tissue and blood cells which renders them more sensitive to the products of the tubercle bacilli.

### VIRUSES

The tissue culture method has been used rather extensively for the cultivation of viruses, beginning with the work of Lambert, Steinhardt and Poor in 1912 and Levaditi in 1913 on the virus of rabies. Levaditi cultivated the virus with ganglionic tissue from normal rabbits and by transferring it to fresh tissue every few days succeeded in keeping the virus potent for thirty days. He also succeeded in keeping the virus of poliomyelitis potent through many passages, in cultures of ganglions from an infected monkey.

More or less success has also been attained in the cultivation or preservation of the viruses of herpes, rabbit myxoma and the rickettsia of typhus fever and Rocky Mountain spotted fever for short periods with suitable tissues.

The most successful efforts have been those of Lambert and his co-workers (1913, 1914), Harde (1915), Gins (1916), Parker (1924), Parker and Nye (1925, 1929), Hach (1925), Cracium and Oppenheimer (1926), Carrel and Rivers (1927) and Haagan (1928) with the vaccine virus.

Lambert and his co-workers, Steinhardt and Israeli, laid small pieces of cornea of the normal rabbit in the virus for a few minutes and then explanted the pieces into plasma from a normal rabbit. Other cultures were prepared in the same way by using pieces of liver, heart and kidney. The vaccine virus increased in strength in cultures of the cornea, but died out in the cultures of the other tissues. The cultures of the cornea of an immune rabbit and the cultures of that of an inoculated normal rabbit were explanted into the plasma from an immune rabbit. Both the immune cornea and the immune plasma inactivated the virus. Lambert



and Harde found that the virus died when the tissue culture cells died and that the virus was inactive in those cultures in which for some reason the cells did not grow.

Parker (1924) used the virus-infected testes of the rabbit in normal plasma and added from every five to seven days fresh normal testis. The virus remained potent for fifty-four days through nine passages. He found Guarnieri's bodies in the tissues. Parker and Nye (1925) placed pieces of normal testis in vaccine from the testicle of the rabbit for five minutes and then made cultures in normal plasma, and by adding fresh rabbit testis every five to seven days they kept the virus potent; on the eleventh passage it was 51,000 times more potent than the original virus. After four months, however, the potency was lost.

Cracium and Oppenheimer cultivated the virus of calf vaccine for seventy-one days and found that the virus was bound up in some way with granules, the so-called Paschem bodies, which were obtained by centrifugating the lymph for from forty to sixty minutes. Carrel and Rivers were able to "step up" the potency of the virus by cultivating it with cornea or skin or brain of six to fourteen day chick embryos in a medium of chicken plasma and embryonic juice. More recently, Haagan (1928) succeeded in maintaining the virulence of the virus for eight months. He used infected testis of rabbit explanted into normal plasma with spleen extract as a growth-promoting substance.

The important points brought out by the work in tissue culture of viruses can be summed up as follows: 1. Viruses which become impotent in the course of a few hours in culture mediums at incubator temperature can be maintained and even increased in virulence during a period of several months when cultivated in the presence of living cells. 2. Viruses soon lose their virulence when the cells die. 3. Special types of cells, such as nervous tissue, corneal epithelium, skin and testis, are apparently essential for the cultivation of the special viruses. 4. The vaccine virus is apparently present in the plasma of infected animals and in or on the white blood cells of such animals. 5. There are no indications that the viruses exist in culture mediums at any great distance from the living cells.

#### CHICKEN SARCOMA

There are a number of points which seem to ally the Rous and other similar chicken sarcomas with the virus diseases. The cultivation of the Rous virus in the presence of living macrophages and the dying out of the virus in cultures when the cells die, the presence of the virus in the cell-free blood plasma of sarcomatous chickens and on washed white blood cells, and the transmissibility of the sarcomas by cell-free tumor filtrates and desiccated tumor powder would seem to ally them with the virus diseases and to separate them off from mammalian sarcomas. On the other hand, frequent metastases into the lungs, liver, spleen and heart would seem to indicate that they are related to malignant tumors.

The investigations of chicken sarcomas by means of tissue cultures have been concerned, for the most part, with the morphologic and cultural characteristics of the cells that migrate from the tumors and with the relation of the virus to these cells.

Carrel and Burrows (1910, 1911) obtained in cultures of Rous chicken sarcoma two types of cells, an inner zone of radiating spindle cells and of ameboid round cells, and an outer zone of ameboid round cells that had migrated farther and faster than the spindle cells. They were unable to find any morphologic characteristics differentiating them from normal cells, but tumors were produced when the cultures were inoculated into fowl. Since the spindle cells and ameboid cells were not very different in appearance and behavior from normal cells, it became important to obtain pure strains of the two types of cells and to determine by inoculation which type was malignant. Over ten years elapsed, however, before Carrel, in 1924, isolated in pure cultures the spindle cells or fibroblasts and the ameboid cells or macrophages by utilizing the differential action of serum and embryonic juice. The pure cultures of fibroblasts rarely produced tumors after the fourth passage, while pure cultures of the ameboid cells always produced

tumors when inoculated into chickens. From this Carrel concluded that the macrophage or monocyte was the "malignant" cell. Since the cell-free supernatant fluid from the cultures of the so-called "malignant" cells also produced tumors, and since it is obviously impossible to inoculate the macrophages without inoculating some of the medium, the malignancy of the cultures might equally well be ascribed to a virus that can survive and multiply in the presence of macrophages but not in the presence of fibroblasts.

Fischer (1924, 1926) also obtained pure cultures of chicken sarcoma cells (monocytes) and succeeded in carrying subcultures for over two and a half years without their losing malignancy.

The "malignant" cells according to Carrel are (1) short-lived, fragile and difficult to cultivate; (2) able to digest fibrin rapidly; (3) readily transformable into fibroblasts, and (4) able to reproduce the Rous principle.

Since Fischer succeeded in cultivating the cells for over two and a half years, they can hardly be considered as short-lived cells; nor can they be considered as fragile cells, for Fischer claims to have obtained from a single cell a culture that was carried on for several months. This proliferation of a single sarcoma cell is not due to any special proliferative ability, since, according to Fischer and Laser (1927), malignant tissues multiply less rapidly than normal ones in their cultures. The liquefaction of the plasma clot is one of the most striking differences between tumor tissue and normal tissue. The transformation of the sarcomatous monocytes or macrophages into fibroblasts occurs more frequently, according to Carrel and Fischer, than the transformation of normal monocytes into fibroblasts. Separate cultures of such transformed malignant macrophages are no longer able to reproduce the tumor, according to Fischer. The ability of sarcoma macrophages and of normal ones to bring about the reproduction of the Rous virus in vitro is the most interesting part of the work on chicken sarcoma. Rous and many others had previously shown that the virus loses its activity after suspension for twenty-four hours in a fluid medium. Carrel found that when the Rous filtered extract was added to flask cultures of normal embryonic pulp, of normal spleen or normal buffy coat growing in a medium of plasma, Tyrode solution and embryonic juice, the virus remained active and even increased. When fragments of normal buffy coat or of normal spleen were added from time to time and the cultures transferred every two or three weeks into new flasks, there was produced during a period of two months at least 1 cc. of highly virulent fluid every day. The quantity of active virus depends, according to Carrel, on the number of multiplying cells in the medium, and soon dies out if the cells die.

It has been claimed that normal monocytes and macrophages can be transformed into "malignant cells" by treatment with the following substances:

1. Filtered extracts of chicken sarcomas. Carrel considered that the addition of the Rous virus to cultures of normal macrophages from the spleen or buffy coat transforms the latter into malignant cells because the cultures produce tumors when inoculated into fowl. When the virus or filtered extract was added to the culture medium, free from cells, the virulence was lost after forty-eight hours at incubator temperature. These observations might equally well be explained on the assumption that the virus can survive or multiply in the presence of living monocytes or macrophages.

2. Arsenic. Fischer asserted that normal spleen from a seven day chick embryo cultivated in arsenic pentoxide produced, after a number of passages, malignant cultures that gave tumors when inoculated into fowl. Haagan also reported a somewhat similar transformation of normal monocyte cultures into malignant cultures after treatment with arsenious acid.

3. Tar. Laser reported the transformation of normal embryonic spleen cells into malignant sarcoma cells by cultivating them in plasma from a hen into which tar had previously been injected intravenously.

These astonishing reports on the transformation of normal cells into sarcoma cells by arsenic and by tar in vitro in a relatively short period of time are much in need of ample confirmation.

## MAMMALIAN SARCOMAS

Cultures of mammalian sarcomas usually show in autoplasm or homoplasm two types of migrating cells: ameboid cells, (monocytes or macrophages) and spindle cells (multipolar cells or fibroblasts) (Carrel and Burrows, 1911, Jensen and Ehrlich, sarcomas and a fibrosarcoma in man; Lambert and Hanes, 1911, mouse and rat sarcomas; Lewis and Gey, 1923, Crocker mouse sarcoma no. 180; Policard, 1926, rat sarcoma; Lewis, 1927, Walker rat sarcoma no. 1; Fell and Andrews, 1927, Jensen rat sarcoma; Carrel, 1927, Crocker rat sarcoma no. 10; Carrel and Ebeling, 1928, Jensen rat sarcoma). The migration is somewhat similar to chicken sarcomas and consists of an outer zone of more rapidly moving macrophages and an inner zone of macrophages and spindle cells. The cultures produced, as a rule, more or less rapid liquefaction of the clot. Carrel (1927) and Carrel and Ebeling (1928) obtained pure cultures of fibroblasts from the Crocker rat sarcoma no. 10 by cultivating small fragments of the tumor in a mixture of chicken plasma, Tyrode solution and extract of embryonic chick. The macrophages disappeared after a few passages. When pure cultures of the fibroblasts were inoculated into rats small tumors appeared in from four to six days that developed slowly and finally killed the animal. These pure cultures of fibroblasts continued to proliferate for sixteen months and retained their malignancy during this period.

The spindle cells of the Crocker mouse sarcoma no. 180 differ somewhat from normal fibroblasts; they are larger, the cytoplasm is denser and more granular and the nucleus is large. The fibroblasts of the Walker rat sarcoma no. 1 (Lewis, 1927) show somewhat similar peculiarities and, in addition, according to M. R. Lewis and Lockwood, contain twice the normal number of chromosomes. The fibroblasts of Crocker rat sarcoma no. 10 are likewise generally larger and coarser than normal ones. According to Carrel, the malignant fibroblasts of the Crocker rat sarcoma no. 10 are similar to normal ones in their mode of locomotion, residual activity, duration of life in nonreplanted cultures and in their rate of growth. The colonies of the malignant fibroblasts are larger, as a rule, than those of normal ones, and the malignant fibroblasts liquefy rat plasma, while normal ones do not. They also turn phenol red golden yellow, while normal ones turn it a pinkish orange, indicating that sarcomatous fibroblasts produce more acid than normal ones. Both types of fibroblasts can multiply to an unlimited degree in chick embryonic juice. Calf liver digest will suffice for an unlimited proliferation of sarcoma, but not of normal fibroblasts.

Lambert and Hanes (1911) found that the Ehrlich rat sarcoma cells grew as vigorously in plasma from tumor-bearing animals and from normal animals as in the plasma from six types of immune rats. Similar results were obtained by Lewis (1927) with the Walker rat sarcoma. Tumor cells, like normal cells, often grow readily in plasma or in a mixture of plasmas of alien species. Lambert and Hanes (1911) and Lambert (1914) found that the plasma from guinea-pigs immunized with several subcutaneous injections of rat sarcoma was an extremely poor medium for the culture of rat sarcoma cells and normal fetal rat ectoderm as compared with normal guinea-pig plasma. Similar results were obtained with plasma of guinea-pigs immunized with injections of fetal rat ectoderm. Lumsden (1924, 1925, 1926, 1927) claimed that the plasma from different species of animals into which fragments of mouse or rat sarcoma had been injected becomes highly toxic to the cultures of the antigenic tumor, killing the cells within a few minutes. This toxicity is not entirely specific. Drew found that such serum has an injurious effect on normal tissues such as mouse kidney epithelium.

## MAMMALIAN CARCINOMAS

The epithelial cell of carcinoma has long been considered as the malignant cell of this type of tumor, and its recognition in cultures was comparatively easy, since they migrate in sheets or tubules as do normal epithelia (Lambert and Hanes, 1911; Carrel and Burrows, 1911; Thomson and Thomson, 1914). Drew (1922, 1923), the first one to obtain pure cultures of mouse carcinoma epithelium,

made the interesting discovery that the addition of fibroblasts to pure cultures (pure epithelium plus pure connective tissue) caused the epithelium to form acini and that the whole culture strongly resembled a normal mouse mamma.

The carcinoma cells thus far cultivated apparently show no special morphologic characteristics that would differentiate them from normal epithelium. According to Fischer (1928), cultures of mouse carcinoma cells are more sensitive to changes in the hydrogen-ion concentration of medium than are cultures of normal cells and are far less resistant to changes on the acid side. The carcinoma cells suffer more from loss of oxygen than do normal ones, and Fischer thinks that the relatively high oxygen tension needed by carcinoma cells may be necessary for the decomposition and partial elimination of lactic acid produced in the cultures. Pure strains of epithelial cells from Ehrlich's mouse carcinoma and the Flexner-Jobling rat carcinoma have been cultivated for many weeks and have retained their malignancy. Carcinoma cells, like sarcoma cells, tend to liquefy the plasma clot rapidly.

The cytolytic effects of antiserums on actively migrating mouse cancer cells was tested by Kohn-Speyer.

The effect of x-rays on carcinoma and sarcoma cells in cultures has been studied by Kimura and on normal cells by Strangeways and Oakley and by Strangeways and Hopwood. In both instances, there was a definite diminution in the number of cells undergoing mitosis. The Gamma radiations utilized by Canti and Spear also had a definite effect in reducing the number of cells in mitosis.

## Book Reviews

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ARTHRITIS AND RHEUMATOID CONDITIONS, THEIR NATURE AND TREATMENT. By RALPH PEMBERTON, M.S., M.D., Physician to the Presbyterian Hospital, Philadelphia; Associate Professor of Medicine in the Graduate Medical School of the University of Pennsylvania. Price, \$5. Pp. 354, with 42 engravings and 1 colored plate. Philadelphia: Lea & Febiger, 1929.

Pemberton's monograph is rather loosely knit and has decidedly too much detailed discussion of recent experimental work. Important as much of this material undoubtedly is, a more critical summation would have been desirable. Those who are interested in repeating or elaborating the experiments described must of necessity refer to the original papers, and to others there seems to be an unnecessarily large amount of description of methods. This criticism applies particularly to the section on dynamic pathology which deals with tissue and chemical alterations. To many who are interested in this subject it may also seem that the author's extremely brief summary of the bacteriologic investigations in arthritis, only to speak in considerable detail and at great length of the circulatory changes, sugar tolerance, blood count and other chemical and metabolic abnormalities, is not wholly justified by the present day conception of the arthritic problem.

Nevertheless, much valuable material is contained in this book. Wide clinical experience is manifest throughout. Differences in pathology and symptomatology are adequately discussed with a wholesome warning that the lines between cannot be too closely drawn. The description of the morbid processes in this work as elsewhere is based on the monograph of Nichols and Richardson published in 1909. The chapter on treatment covers 134 pages and is probably as adequate as possible. Surgical and orthopedic measures are touched on briefly as compared with their consideration in Fischer's new book on the same subject. For this there is ample justification considering the breadth of that subject alone.

On the whole, Pemberton's book is a satisfactory expression of the ever gaining attitude that arthritis is a many sided disease requiring continued and utmost endeavor in elucidation and in treatment.

PATHOLOGY FOR STUDENTS AND PRACTITIONERS. Authorized translation of the *Lehrbuch der Pathologischen Anatomie* by DR. EDWARD KAUFMANN, Professor of General Pathology and Pathological Anatomy and Director of the Pathological Department, University of Göttingen. Translated by STANLEY P. REIMANN, M.D., Pathologist and Director of the Research Institute of the Lankenau Hospital, Philadelphia; Assistant Professor of Experimental Pathology in the Graduate School of the University of Pennsylvania. Price, \$30. Three volumes. Pp. LXII, 2452, with 1,072 illustrations. Philadelphia: P. Blakiston's Son & Company, 1929.

Dr. Reimann's translation of Kaufmann's "*Lehrbuch*" makes available to the English-speaking world one of the great textbooks and works of reference in pathology. Indeed it may be said that there is no other work that contains such a wealth of concise information in the field of pathologic anatomy. Written, as Kaufmann states in his introduction to the latest edition, primarily for the student of medicine, the author has handled with special care such subjects as are regarded the most important for those who are to be the future physicians. The treatment of the subjects has by no means been confined to pathologic anatomy, but, to complete the point of view, to make it clearer to the understanding and at the same time to maintain interest, excursions are made into embryology, anatomy, physiology and general pathology. The close connection between pathologic anatomy and practical medicine, between theory and practice is emphasized by numerous references to clinical data. How well the author has succeeded in

his task is shown by the ever-increasing popularity of this work in his own country as well as abroad. Dr. Reimann's translation faithfully follows the German text. The translation, however, has somewhat rearranged the divisions and subheadings, and the publishers have used a better type and better paper in the translation. Thus the work has been expanded from the original two into three volumes. For greater convenience, a complete index of sixty-two closely printed, double columned pages is included in each volume; the references to illustrations are in bold-faced type. While there is a complete system of cross-references to related subjects in the text, the index summarizes them for ready references. The exhaustive bibliography which takes up more than 200 pages of the third volume is a veritable treasure mine of information. There are references to the literature of nearly all civilized countries. In the majority of the citations, the full title of the paper quoted is given. In many instances, Kaufmann gives in a few words the essentials of the paper; thus a quotation is followed by the remark "Confirms Aschoff's views"; "The diagnosis of catarrhal icterus should be limited; primary injury to liver cells must be considered"; "The stomach had become invaginated into the duodenum, woman of 58, good picture." The scope of the work may be judged from the table of contents: I. Organs of Circulation, pp. 1 to 184; II. Blood and Lymph: Hematopoietic Organs, pp. 185 to 291; III. Respiratory Organs, 292 to 542; IV. Digestive Organs, 543 to 816; V. Osseous System, 817 to 1050; VI. Joints, 1051 to 1227; VII. Adrenal Glands, 1276 to 1291; VIII. Urinary Apparatus, 1292 to 1457; IX. Sex Organs, 1458 to 1803; X. Nervous System, 1804 to 2031; XI. Muscles, 2032 to 2060; XII. Tendon Sheaths and Bursae, 2061 to 2067; XIII. Skin, 2068 to 2224; Appendix (References to the Literature), 2225 to 2452; Index, I to LXII. The treatment of the various subjects is thorough, systematic and yet concise. The translator has done far more than render Kaufmann's "Lehrbuch" into readable English. He has enriched the work by more than 100 excellent illustrations, and throughout the books there are numerous additions, partly references to the newer American literature, partly personal views of the translator. The reviewer believes that the English-speaking medical world owes a debt of gratitude to Dr. Reimann for doing so well a laborious, but well worth while task.

**THE SCIENTIFIC METHOD: ITS FUNCTION IN RESEARCH AND EDUCATION.**  
 TRUMAN LEE KELLEY, Professor of Education and Psychology, Stanford University. Price, \$2.50. Pp. 195. Columbus, Ohio: The Ohio State University Press.

This little book contains five stimulating lectures on topics suggested by the title. The main subjects are the relation of method to the field of investigation, the function of the questionnaire, the units for measuring intelligence and achievement, the bearing of recent developments in science on problems of education and the mental traits of men of science. Pathologists will find the discussion of the fundamental principles of scientific research and the generalization of the mental traits of men of science especially interesting and valuable. The author has a fortunate gift of clear, vivid, often aphoristic statement. It is an admirable book that should be read by all who are concerned seriously with scientific research.

## Books Received

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**TULAREMIA: HISTORY, PATHOLOGY, DIAGNOSIS AND TREATMENT.** By Walter M. Simpson, M.D., Director of Diagnostic Laboratories, Miami Valley Hospital, Dayton, Ohio. Foreword by Edward Francis, Surgeon, U. S. Public Health Service. Price, \$5. Pp. 162, with 53 illustrations and 2 colored plates. New York: Paul B. Hoeber, Inc., 1929.

**GREEK MEDICINE.** Being Extracts Illustrative of Medical Writers from Hippocrates to Galen. Translated and annotated by Arthur J. Brock, M.D. (Edinburgh), translator and commentator of Galen, etc. Price, \$1.75. Pp. 256. New York: E. P. Dutton & Company.

**THE FEMALE SEX HORMONE.** By Robert T. Frank, M.D., Gynecologist to Mount Sinai Hospital, New York. Price, \$5.50. Pp. 324, with 86 illustrations and 36 graphs. Springfield, Ill.: Charles C. Thomas, 1929.

**PRÄKTIKUM DER KLINISCHEN, CHEMISCHEN, MIKROSKOPISCHEN UND BAKTERIOLOGISCHEN UNTERSUCHUNGSMETHODEN.** Ninth edition. By M. Klopstock and A. Kowarski. Price, 14 marks, bound. Pp. 524, with 51 illustrations and 25 colored plates. Berlin and Vienna: Urban & Schwarzenberg, 1929.

In this useful book, the practical methods employed in clinical chemistry, microscopy and bacteriology (including the commoner serologic tests) are described clearly and briefly. Histologic methods are not included. In this edition many parts have been revised and several recent methods introduced. The illustrations also have been improved and new ones added.

**PETTIBONE'S TEXTBOOK OF PHYSIOLOGICAL CHEMISTRY, WITH EXPERIMENTS.** Revised and rewritten by J. F. McClendon, Ph.D., Professor of Physiological Chemistry, Medical School, University of Minnesota, Minneapolis. Fourth edition. Price, \$3.75. Pp. 368. St. Louis: C. V. Mosby Company, 1929.

**THE BLOOD PICTURE AND ITS CLINICAL SIGNIFICANCE (INCLUDING TROPICAL DISEASES).** A Guidebook on the Microscopy of Blood. By Prof. Dr. Victor Schilling, Physician-in-Chief, The First Medical University Clinic, Charité, Berlin. Translated and edited by R. B. H. Gradwohl, M.D., Director of the Pasteur Institute of St. Louis, and the Gradwohl School of Laboratory Technique, St. Louis. Seventh and eighth revised edition. Price, \$10. Pp. 408, with 44 illustrations and 4 colored plates. St. Louis: C. V. Mosby Company, 1929.

# ARCHIVES OF PATHOLOGY

VOLUME 8

DECEMBER, 1929

NUMBER 6

## VASCULARIZATION OF THE THORACIC AORTA\*

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TORONTO, CANADA

Since Köster drew attention to the relation between the vasa vasorum and the localization of arterial disease, their importance in this rôle has frequently been noted. Ebner and Meigs, following Köster, demonstrated the increasing vasculature of the walls of the blood vessels with disease and the varied manner of advance in different lesions. More recently, Klotz<sup>1</sup> has suggested that the localization of syphilitic lesions in the ascending aorta might have an anatomic basis. He believed that the distribution of inflammatory states within the arterial coats was directly dependent on the vascularity of the walls, and that the senile degenerations of the media were the result of cell starvation, since they were observed distant from the vasa and the intima. Wearn, who found a rich supply of vasa vasorum arising from a coronary branch distributed to that portion of the aortic wall where aortitis is most common, suggested that this relation might have an important significance.

The vasa vasorum of the aortic wall, their origin and anastomoses have been noted for several centuries. Haller<sup>2</sup> mentioned Thomas Willis as one of the first to observe them. The former described them as arising from the right and left coronaries or an accessory coronary, and forming a network in the adventitia of the ascending aorta. This network gives off branches to the media and to the intima; to the pulmonary vasa laterally; to the pericardial vessels and the vasa of the arch above. He described a wide anastomosis between the coronary and the bronchial arteries through the vasa of the pulmonary artery, and the pericardial, internal mammary, inferior thyroid, esophageal and intercostal vessels through the vasa of the ascending aorta. Cruveilhier,<sup>3</sup> Béraud, Langer and lately Gross<sup>4</sup> also observed these

\* Submitted for publication, July 22, 1929.

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1. Klotz: *Arteriosclerosis, Studies from the University of Pittsburgh*, 1911; *Tr. A. Am. Phys.* **27**:181, 1912; *J. Path. & Bact.* **18**:259, 1913; *J. M. Research* **31**:409, 1915.

2. Haller: *Elementa Physiologia Corporis Humani Lausanne*, 1757, vol. 1, pp. 67-89.

3. Cruveilhier: *Descriptive Anatomy*, London, 1842, vol. 2, p. 670.

4. Gross: *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects*, New York, Paul B. Hoeber, 1921; *J. Lab. & Clin. Med.* **13**:257, 1927.



anastomoses. The vasa of the arch and of the descending limb of the thoracic aorta were described as arising from the aortic lumen or from branches of the bronchial, internal mammary, subclavian, esophageal and intercostal arteries.

Later descriptions agreed closely with Haller's. However, the manner of distribution of the vasa vasorum in the aortic wall proved a debatable point. Bichat <sup>5</sup> found them always ending in the outer third of the media; Meckel found them penetrating to the intima, while Crisp <sup>6</sup> found them ramifying between the adventitia and periadventitia to pierce the media only. Finally, Köster, Ebner, Meigs <sup>7</sup> and Klotz described the vasa vasorum in normal arteries as not passing the outer third of the media, but in disease proliferating and penetrating the inner media to reach the intima.

In 1926, Woodruff <sup>8</sup> found vasa vasorum in the aorta of the horse extending to the intima. In the ascending limb of the dog's aorta, the nutrient vessels were found arising from the lumen directly by discrete openings. One of these was found to anastomose freely with vasa from one of the coronary arteries.

There remains the task of more accurately ascertaining the vascularization of the thoracic aorta, and relating its anatomic character with the processes in disease.

#### TECHNIC

To accomplish this, the hearts and aortas of dogs, lambs and human beings were studied.

The hearts were injected by aortic cannulae so that the first coronary branches which gave vessels to the aorta were always filled. Celluloid masses of various viscosities were employed, in which finely ground, opaque and colored materials were suspended. An initial air pressure of 300 mm. of mercury suddenly applied was gradually reduced to 150 mm. mercury at the end of one-half hour. Cannulas were then inserted into the coronary vessels, a cinnabar celluloid suspension was injected into the right, and a Berlin blue celluloid suspension into the left, until all large vessels were well filled.

The aortic vessels were filled by injection from the aortic lumen. Glycerin gelatin masses were employed in which finely ground, opaque and colored materials were suspended. An air pressure of 400 to 800 mm. mercury was used. The gelatin was allowed to set while pressure was maintained, so that any untied leaks were stopped while the vessels remained filled.

Radiography, dissection of cleared and uncleared specimens and corrosion of specimens were carried out. Serial sections gave the details of the distribution of the vasa vasorum and other fine vessels.

#### RESULTS

From the data furnished by these experiments, the thoracic aorta may be roughly described as vascularized by a sheath of areolar con-

5. Bichat: *General Anatomy*, Boston, 1822, vol. 1, p. 317.

6. Crisp: *The Blood Vessels*, London, 1847, pp. 3-4.

7. Meigs: *Human Blood Vessels*, 1907, vol. 2, pp. 25, 70 and 75.

8. Woodruff: *Am. J. Path.* **2**:567, 1926.

nective tissue richly supplied with blood vessels. This extended from the heart to the diaphragm and below over the abdominal aorta. Over the arch and the descending thoracic limb, this sheath contained at least two distinct layers of interweaving vessels which were derived from vessels of adjacent structures or from branches of the aortic efferent vessels. Over the ascending limb, only a single network was usually seen, derived from coronary branches, from cardiac fat-pad branches of these and from descending vessels of the aortic arch. The adventitial vessels in each case were largely furnished by these anastomotic networks. At the root of the aorta the richest vascular bed was found. The ascending limb was most vascular along its convex border, the arch and the descending limb on their posterior surface.

In order to bring out more clearly the differences in vascularity between the various portions of the thoracic aorta, the features of vascularization common to lamb, dog and man will be described under the headings of ascending limb, arch and descending limb. Points of variance between these mammalian types and interesting differences of vascularization will be noted.

*Ascending Limb of Aorta.*—The vessels of the ascending limb of the thoracic aorta formed two richly anastomosing networks: one in the connective tissue and fat beneath the visceral pericardium, the other in the adventitia.

The vessels of the periadventitial network usually arose from the first two pairs of branches of the right or the left coronary artery, from branches of these vessels which ran to the conus arteriosus and the pulmonary artery anteriorly, and along the auriculo-aortic grooves and to the superior auricular surfaces posteriorly, or from accessory coronary vessels. From above, the vasa of the arch and the pericardium descended from the pericardial reflection to anastomose extensively with the vessels from below and with aortic branches of the bronchial arteries on the pulmonary artery near its bifurcation (figs. 1 and 2).

From the right coronary artery, the first pair of branches usually ran upward to spread anteriorly and posteriorly over the ascending limb (fig. 1). The anterior branch spread in the aortic pulmonary groove and then over the pulmonary artery, where it frequently anastomosed with pulmonary branches of the left coronary artery. It anastomosed above with vessels encircling the middle third of the ascending limb (fig. 1 *A* and *B*). The posterior branch also anastomosed above with the last mentioned vessel and behind with ascending vessels from the region of the aortic auricular groove (figs. 1 and 2).

The second pair of branches also spread anteriorly and posteriorly (fig. 1). The anterior branch usually constituted the arcuate branch

described by Gross <sup>4</sup> as being the first anterior right coronary division. It supplied the region of the conus arteriosus and anastomosed with a similar branch from the left coronary artery and with adjacent vessels above and below. From it many small branches spread on the wall of the ascending aorta over the anterior sinus of Valsalva. It supplied the fat pads of this portion of the heart with an abundant network of arteriae telae adiposae. The posterior branch usually constituted the ramus ostii cavae superioris of Gross (fig. 1 *D*). It furnished the root of the aorta with many small branches and supplied several vessels to the aortic wall over the right posterior sinus of Valsalva. These

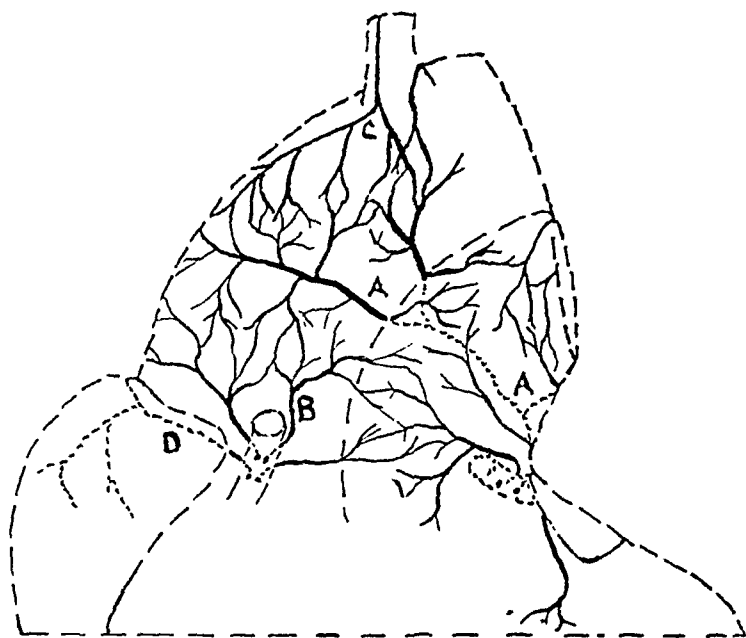


Fig. 1.—The periaortic network of the ascending aortic limb, anterior view.

latter anastomosed above with the left coronary branch encircling the ascending aorta at its middle third, and anteriorly and posteriorly with nearby aortic vessels.

From the left coronary artery, the first pair of branches usually ran upward and laterally (fig. 2). The anterior branch crossed the aortic pulmonary groove to spread on the pulmonary artery, finally anastomosing with the right coronary branches described. It gave many small twigs to the aortic wall in the region of the aortic pulmonary groove. The posterior branch was generally short. It anastomosed with the vessels arising from the auriculo-aortic groove and with larger vessels above. It supplied an area of the aortic wall a little larger than that lying over the posterior half of the left posterior sinus of Valsalva.

The second pair of branches ran upward and again anteriorly and posteriorly. The anterior branch was found in adult human hearts to

be the largest supplying the aortic wall. It ran at first laterally through the fat about the left coronary opening to the aortic pulmonary groove. Here it turned upward in the areolar connective tissue between the two vessels, and gave numerous branches to each, finally spreading anteriorly on the middle third of the aorta and the pulmonary artery. The former it almost encircled, by passing over its convex surface to unite freely with posterior branches of the left coronary artery over the left posterior sinus of Valsalva. An extensively anastomosing circle of vessels about the middle third of the ascending limb was thus formed (figs. 1 *A* and 2 *A*).

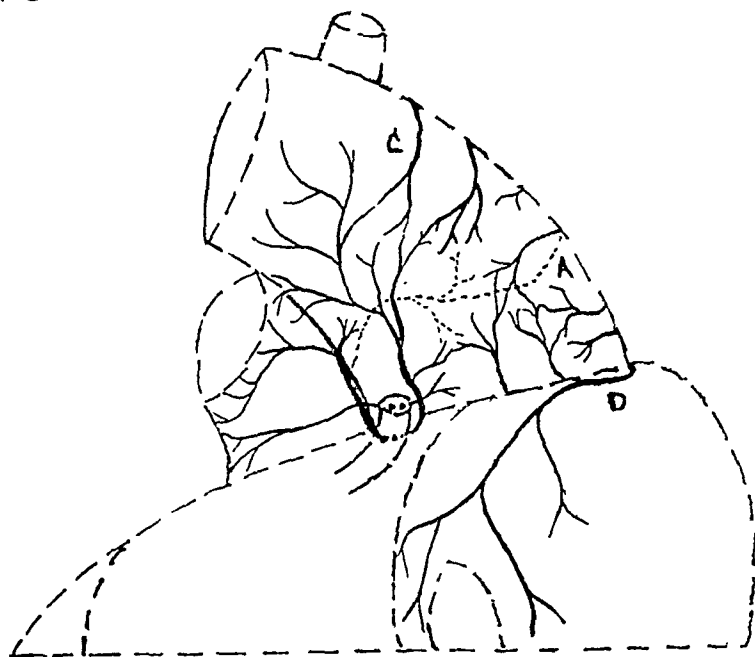


Fig. 2.—The periaortic network of the ascending aortic limb, posterior view.

The posterior of this second pair of left coronary branches ran almost directly upward from its origin and paralleled the aortic pulmonary groove. It ended just below the pericardial reflection, anastomosing with its vessels and with those on the posterior surface of the aortic arch. It also sent branches laterally into the aortic pulmonary groove and over the pulmonary artery to the left and right, to anastomose with vessels on the convex border of the ascending aorta (fig. 2 *A* and *C*).

From above, the largest vessels descended from the aortic arch (fig. 1 *C*) beneath the pericardial reflection down the convex aspect of the ascending aorta, their branches spreading toward the concave surface and anastomosing with the ascending coronary branches. This anastomosis was especially marked with the left coronary branch which

encircled the middle third of the aorta. Smaller branches from the pericardium and from the posterior surface of the aortic arch and a few bronchial branches on the pulmonary artery descended to anastomose with the vessels described.

The most abundant periadventitial supply to the ascending limb was on its outer aspect. It was considerably less on the posterior aspect and diminished also from below upward, so that the root of the aorta was more abundantly supplied than the portion adjacent to the arch.

As to the variations in the vasculature before noted, the most important was found in the lamb hearts. In these, the large branch from the left coronary, so prominent in man, was small, while the pulmonary vasa and the right coronary branches to the aorta were relatively increased in size. Children's hearts frequently showed this. Dogs nearly always had a preponderance of vasa from the right coronaries. This was accounted for in two cases by the finding of small vasa which arose directly from the lumen of the ascending limb.

The arcuate branch which crossed the junction of the pulmonary artery and the conus arteriosus arose in several human and lamb hearts as the first anterior right coronary branch. It sent branches upward over the ascending aorta which took the place of those usually arising as the first anterior right coronary branch (fig. 1 *B*).

The ramus osteii cavae superioris usually arising as the second posterior right coronary branch was in two lamb hearts and one human heart given off first. It then supplied branches to the ascending aorta which took the place of those that have been described as arising from the first posterior right coronary branch. In one lamb and one human heart it arose from the left coronary as its second branch. It then gave off the vessels which ran over the left posterior sinus of Valsalva and upward just posterior to the pulmonary aortic groove and those described as arising in the auriculo-aortic groove to ascend the posterior aortic wall. The posterior right coronary branches to the aortic wall and the anterior superior aspect of the right auricle were increased in size.

In several hearts a right, and in one heart a left, accessory coronary vessel supplied the areas usually provided for by one or more of the first two pairs of coronary branches.

The adventitial network of the ascending limb was formed by branches of the right and of the left coronary artery below, by branches from the periadventitial network and from the adventitial vessels of the arch. They arose from the first four right and left coronary branches as fine vessels, at first in the cardiac fat pads, later ramifying above in the adventitia. In this, they spread on the ascending aorta over an area corresponding to the anterior and the left posterior sinuses of Valsalva, anastomosing above with the vessels given off by the

periadventitial network. At the root of the aorta, vascularization was most abundant over the anterolateral aspect and least abundant behind over the right posterior sinus of Valsalva.

Finally, the outer third of the media was supplied by branches of those networks which penetrated it at right angles, to spread laterally and longitudinally between the elastic lamellae. These branches anastomosed freely. They were largest and more closely grouped near their parent vessels. Those more distant were smaller, had longer branches with fewer anastomoses and were obliged to supply a greater portion of the aortic wall. The medial vessels were grouped more closely and were more numerous at the convex surface and about the root of the aorta over the region of the left posterior and the anterior



Fig. 3.—The periadventitial network of the arch of the aorta, anterior view.

sinus of Valsalva. They were most numerous immediately beneath the adventitial or periadventitial vessels, diminishing in number between them.

*Arch of Aorta.*—The periadventitial network of the arch could be divided into two layers: one in the areolar connective tissue, the other lying on the adventitia.

The outer periadventitial network arose superiorly from branches of the innominate, left carotid and subclavian arteries which descended and ramified over it. These branches arose at various distances above the arch, usually at least half an inch (1.27 cm.). The largest vessel descended from the right anterolateral surface of the innominate artery to ramify on the convex surface of the ascending limb as described (figs. 2 and 3). The branches from the other great vessels were smaller and were less numerous especially toward the descending portion of the arch. Posteriorly, a thick periadventitial network was

formed, deriving its vessels from the inferior thyroid arteries, the esophageal and upper intercostal branches of the aorta and the bronchial arteries. The superior and the posterior periadventitial vessels terminated or anastomosed with each other along the midline of the anterior aortic surface.

The inner periadventitial network was formed by branches of the outer group. About the great vessels of the neck and the first pair of intercostal vessels, however, branches were given to it directly. Its larger vessels followed the course of those in the layer above, although they were usually not found lying directly beneath them. They anastomosed frequently, forming loops about the roots of the great vessels.

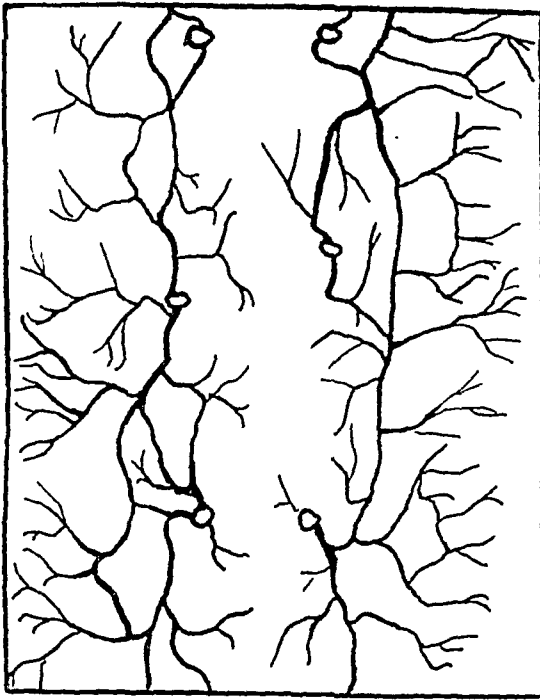


Fig. 4.—The distribution of the vessels of the descending thoracic limb of the aorta: outer periadventitial network.

The vasa vasorum were finally derived from these two outer networks to form an adventitial network and then penetrated the outer third of the media as described. They were most numerous beneath the periadventitial ramifications.

The vascularity of the arch was greatest on the convex surface of its ascending portion, and on the posterior surface of its transverse portion (fig. 3). It was least vascular on its anterior surface, particularly toward its descending portion. This latter section was most vascular on its posterior aspect, resembling the descending thoracic limb in this respect.

*Descending Limb of Aorta.*—The two periadventitial networks of this portion were formed by vessels which usually arose from the branches of the aorta at least 2 mm. beyond its adventitia. The inferior thyroid arteries and the periadventitial vessels of the arch supplied the upper end of the descending limb with many branches.

The more superficial network spread from vessels which looped longitudinally between each pair of intercostal vessels (fig. 4). Their branches ramified laterally over the anterior aortic wall, and for a short distance toward the midline of the posterior wall. Longitudinally there was extensive anastomosis. Fluid injected into the upper intercostals often appeared in one of the lower intercostal mouths. Laterally.

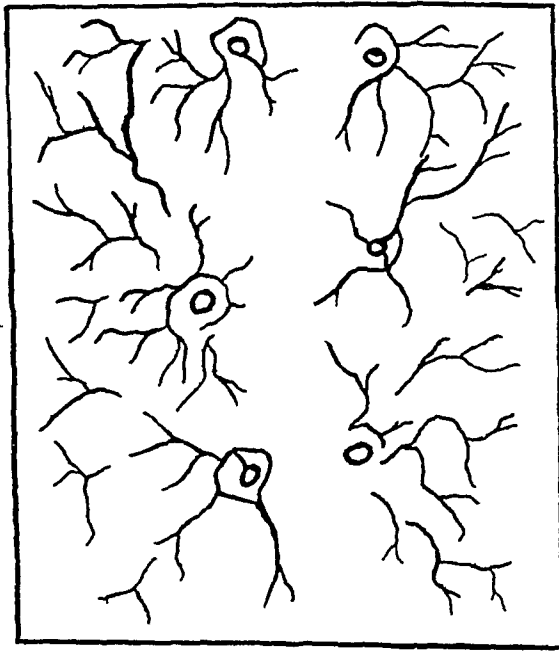


Fig. 5.—The distribution of the vessels of the descending thoracic limb of the aorta: inner periadventitial network.

the ramifications over the anterior wall of the aorta did anastomose, but not so plentifully.

This outer periadventitial network supplied vessels to the inner, the vessels of which ran over the adventitia paralleling closely the larger vessels from which they arose. They formed vascular collars about the aortic vessels (fig. 5). From these they received many branches, given off usually 2 mm. beyond the adventitia as described, and running back to spread on the aorta and encircle the parent vessel. No individual vessel of this deeper network could be followed for more than a short distance, but together they formed a network approximating in appearance the more superficial one. Longitudinally, anastomoses



were extensive, but in the specimens studied the network was not continuous laterally for more than a few centimeters.

From these vascular networks, the adventitia and the media were vascularized by branches forming a network in the adventitia, this in turn supplying the outer third of the media as described. The most numerous branches to the media surrounded the smaller branches of the aorta, particularly the intercostals. Here they formed several anastomosing sheaths and arborescent groups about each vessel. Some of the branches lay in the adventitia between the media of the aorta and that of its efferent branches, to spread in the media and almost reach the

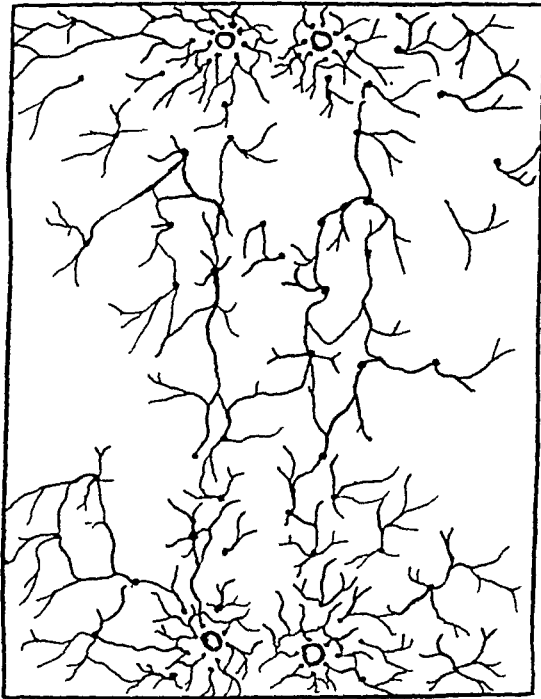


Fig. 6.—A diagram illustrating the distribution of the vasa vasorum of the descending thoracic limb to the media (cut on the flat).

intima; none accomplished this in healthy tissue. Others pierced the media at intervals of from about 20 to 60 microns, and as the distance from the efferent vessel increased, these intervals became greater. Also the number of penetrating vessels decreased, their longitudinal and lateral branches between the elastic fibers increasing in length. Over the posterior wall of the aorta at points central to the efferent branches the number of vessels was least and their separation greatest. Beyond the posterior aspect of the aorta a similar vasal supply to the media was seen, while anteriorly there were barely half as many of these branches in a low power field as there were in a line connecting two of the intercostal branches (figs. 6 and 7).

The descending aortic limb and its connective tissue sheath were most abundantly supplied with vessels, along two longitudinal strips just lateral and parallel to the efferent vessels. The vasa vasorum were most numerous beneath these areas and also in regions encircling each efferent vessel.

The vasa of the thoracic aorta have been described as usually arising from its branches, and the vessels penetrating to the media as arising from the adventitial network. Several variations in this arrangement were found.

The discrete openings in the ascending aorta of the dog, found by Woodruff,<sup>8</sup> were noted in two dogs. They were situated on the right

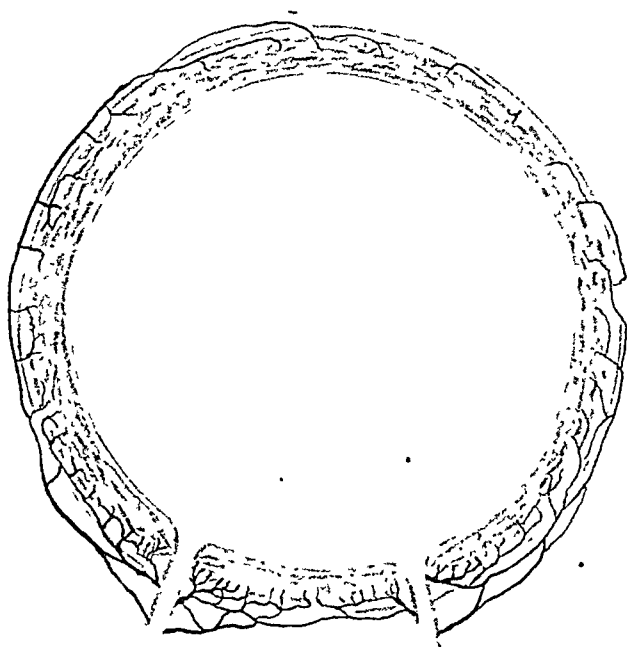


Fig. 7.—A diagram illustrating the distribution of the vasa vasorum of the descending thoracic limb to the media, as seen in a cross-section of the thoracic aorta.

anterolateral surface of the aortic wall, in an area occupying longitudinally the middle third of the ascending limb. Three of the vessels ran from the intima to the vasa arising from the coronary arteries and the aortic arch. Two of them pierced the intima to spread in the media.

The vasa described in the aorta of the horse by Woodruff as penetrating as far as the intima were not found in this study except when the media and the intima were diseased. Atheromatous areas of the intima were frequently completely encapsuled by vessels penetrating from the media. However, two sections from human aortas showed minute nutrient vessels penetrating the intima and branching in the inner third of the media.

Frequently, the vasa vasorum arose from the branches of the aorta while passing through its wall. This they entered at the junction of the media and the adventitia to send branches into the media and along the adventitia to anastomose with the other vasa. The media was not penetrated directly by these branches (fig. 7).

The periadventitial vessels were frequently found to send branches to the media directly. These branches, after giving off their adventitial branches, spread out in the media.

#### COMMENT

The foregoing description of the vascular distribution to the aorta is of interest in relation to the localization of aortic disease. Aneurysm was stated by Osler<sup>9</sup> to be most frequent on the convex border of the ascending aorta and on the posterior part of the arch and the descending limb. Klotz found, in a study of autopsies in 501 cases with aneurysm, that in 207 the lesion occurred on the ascending limb, in 86 on the arch and in 36 on the descending limb of the thoracic aorta. Aneurysm is thus most frequent where vascularization is most abundant.

The blood stream itself is not necessarily the direct carrier of injurious agents. Klotz showed that in syphilitic aortitis, which is the disease most frequently met with in the ascending limb and the arch of the aorta, the infection is carried to the wall by the lymphatics following the blood vessels of the aorta. In general, the distribution of the lymphatics of the aortic wall follows closely that of the vasa vasorum.

Nodular endarteritis appears in the descending aorta and becomes most advanced about the intercostal openings. The posterior border of this portion of the aorta is the site second in frequency. In these areas the vasa vasorum are most abundant.

The appearance of adolescent or early adult aortas showing superficial fatty streaks suggests a relation between the vasa vasorum and the localization of intimal fatty change. The aortas show the fatty deposit most prominently at the intercostal openings and along the base. In the latter region, they delineate the longitudinal lines between the intercostal orifices beneath which the vasa vasorum are most abundant (fig. 4). When chronic nodular endarteritis has thickened the intima around the intercostal openings, these areas are fat-free. As middle life is approached or as aortic disease becomes advanced, superficial fatty streaks are less frequently seen. Only remnants of former fatty deposits appear about the intercostal openings or over patches of intimal and medial fibrosis and degeneration. This is possibly due to a deple-

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9. Osler and McCrae: Principles and Practise of Medicine, New York, P. Blakiston's Son & Company, 1926, p. 869.

tion of the fluid exchange in these regions, the outcome of the fibrosis of antecedent aortic lesions.

Glasunow in his imbibition experiments showed that the dye was absorbed most readily on the posterior wall, along the longitudinal lines delineating the vasa vasorum between the intercostal arteries. Some of his specimens closely resembled adolescent aortas with superficial fatty streaks.

It is probable that the localization of intimal lesions of toxic, nutritional or metabolic origin depends on the variations in absorbing power of different regions of the inner aortic wall. The latter, in turn, seems to be determined by the degree of vascularization.

The medial changes characteristic of toxic and infectious conditions of the aorta are most frequent near the intercostal vessels and about the vasa vasorum. Whether the lesion is primarily lymphatic or vascular is not always ascertainable. In either case, distribution of the vasa vasorum seems to determine the localization of the lesion. In adventitial lesions, this observation has been commonly made.

The senile changes of the media are most frequent where the basal supply is least. As Klotz pointed out, this probably depends on the decreased nutrition of these areas.

#### SUMMARY

The vascularization of the thoracic aorta has been described, and its relation to disease discussed.

Blood vessels are found to be most numerous in the aortic wall where aortic disease, other than senile change, is the most commonly localized.

A relation exists between the presence of certain lesions of the aortic wall and the distribution of the vasa vasorum.

The technic here outlined differed from the methods<sup>10</sup> formerly employed, in that the pigment and radio-opaque material was in the form of a stable suspension. The coronary branches to the ascending limb of the aorta were not occluded by coronary cannulae and were therefore filled and demonstrable.

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10. Campbell: *Quart. J. Med.* **86**:247, 1929. Whitten, M. B.: Review of Technical Methods of Demonstrating Circulation of Heart; Modification of Celluloid and Corrosion Technic, *Arch. Int. Med.* **42**:846 (Dec.) 1928.

# AN UNUSUAL TYPE OF TRIATRIAL HEART\*

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The unusual degree to which congenital defects of the heart have interested both laboratory and clinical workers is attested by the voluminousness of the literature on the subject. The fact that many of the seemingly innumerable communications are scattered in publications difficult of access makes one hesitate to state that any cardiac anomaly, no matter how unique it seems, has not been previously seen and perhaps carefully described; but a diligent search of the literature has not yielded any instance of the peculiar malformation recently presented by a patient at the Babies and Childrens Hospital of Cleveland. Its apparent uniqueness as far as structural conditions and course of circulation are concerned and especially its interesting embryologic bearings seem to make it worth adding to the many bizarre distortions of normal heart development already on record.

## REPORT OF CASE

*Clinical History.*—A white girl, 3 months of age, the second of two children, had been born at full term, weighing  $6\frac{1}{2}$  pounds (2.9 Kg.). Abnormally rapid respiration and cyanosis had been constantly present since birth. For two days prior to admission, fever, irritability and frequent green stools had been noted.

The child was undernourished, weighing but 3.9 Kg. On admission, the temperature was 38 C. (100.4 F.), rising in the next few hours to 40 C. (104 F.). Cyanosis was extreme, especially in the mucous membranes and in the extremities, which were noticeably cold. Respiration was rapid, shallow and panting. The rate varied, with marked, irregular, periodic tachypnea. There was slight retraction of the head, but no rigidity. Mucopurulent material was found in the fauces, and one ear drum was slightly hyperemic.

The veins of the neck were prominent. The liver extended to the umbilicus. The chest showed scattered moist râles, most pronounced at the left base, with harsh breath sounds over the entire chest, especially posteriorly. At the angle of the left scapula, the breath sounds were bronchial. The percussion note was resonant, except for an area of impairment at the left apex anteriorly.

Cardiac activity was increased in intensity and extent. A systolic impulse and diastolic impact were palpable over the right ventricle. The area of cardiac dullness extended from 1 cm. to the right of the right sternal margin to slightly outside the left midclavicular line at the fifth rib. The upper border of dullness was continuous with the areas of impaired resonance at the left apex. A widely distributed, loud systolic murmur was most pronounced just to the right of the apex

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\* Submitted for publication, Sept. 26, 1929.

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pulsation. The rate was rapid, and tick-tock sounds like those usually associated with cardiac anomalies were heard. The blood was of a darker color than could be registered with a Tallqvist scale, and showed a white cell count of 20,000. The urine showed a trace of albumin.

Roentgen examination showed the heart shadow to be globular. The hilums showed increased shadows, presumably due to either bronchopneumonia or pulmonary hyperemia.

Dyspnea became progressively more marked, and the patient died thirty-three hours after admission. The diagnosis, both clinical and roentgenologic, was congenital defects of the heart.

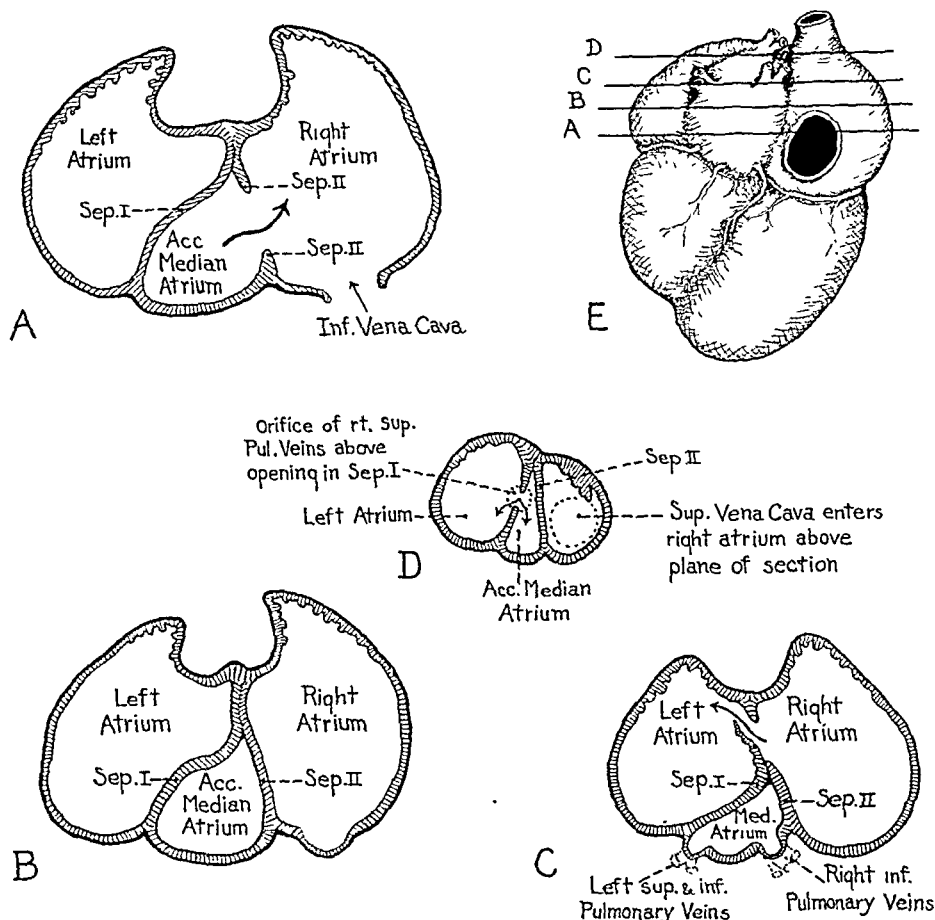


Fig. 1.—Diagrams illustrating the relationships of the accessory median atrial chamber. The lines *A* to *D* on the sketch of the dorsal aspect of the heart show the levels of the accompanying schematic cross sections. Note that three coronary veins, as well as the pulmonary veins, open into the median chamber. A coronary valve fairly normal in appearance and location (compare with fig. 2) covers nothing but a blind pocket at the point where the coronary sinus should appear. The septums have been labeled with their embryologic names, septum primum and septum secundum.

*Necropsy.*—Aside from the conditions in the heart, which are described in detail later, the following positive observations were made post mortem: generalized livor mortis, peritoneal fluid containing a few shreds of fibrin, bilobed right lung with some areas of atelectasis and a left lung of normal configuration but with extensive atelectasis. The liver was large and showed some evidence of

chronic congestion. Similar changes were present also in the spleen. The intestinal tract showed some hyperplasia of the lymphoid structures, with slight irregular injection of the mucosa. No other pathologic conditions were found.

The heart weighed 51 Gm. Externally, it showed a marked dilatation of the right ventricle and a definitely enlarged pulmonary trunk. Viewed in dorsocaudal aspect, it revealed a median bulging of the atrial region marked off on either side by fairly definite lines of depression (fig. 1 *E*). When the heart was opened, this dilatation was found to mark the presence of an accessory median atrial chamber. The external depressions bounding it were indications of the attachments of septums separating this accessory chamber from the right and left atria, respectively.

The accessory chamber was roughlyly wedge-shaped, with its bulging base presenting on the dorsocaudal wall of the atrium and the apex of the wedge directed ventrocephalically (fig. 1). Both left pulmonary veins opened by a common funnel into this median chamber, as did also the group of three right inferior

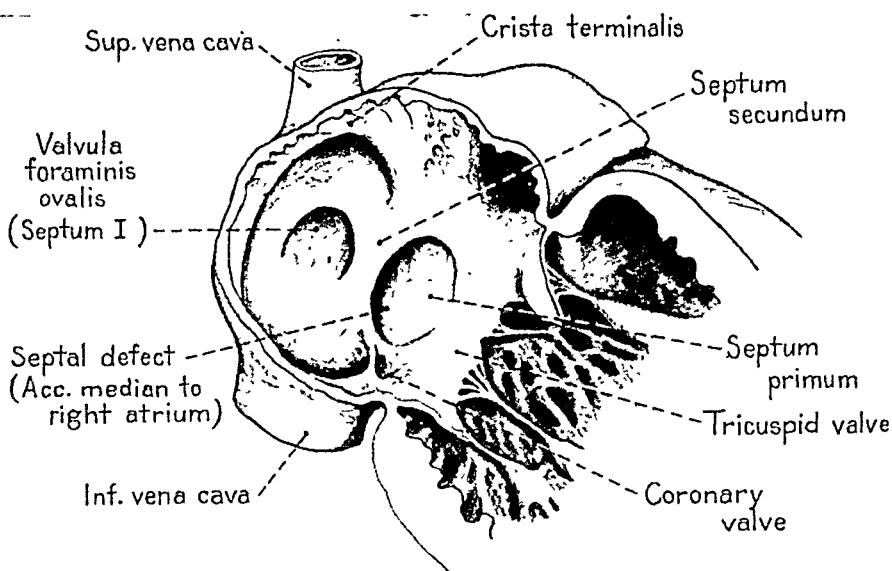


Fig. 2.—Drawing of the heart opened to show the interior of the right atrium. The defect in the septum which separates the median from the right atrium, allows one to look into the median atrium and see the septum which separates it from the left atrium (fig. 1 *A* may be compared here). This septum which forms the left wall of the median chamber exhibits the relations to the atrio-ventricular canal septum which are absolutely characteristic of septum primum in the embryonic heart.

pulmonary veins (fig. 1). The right superior pulmonary veins entered near the apex of the wedge, astraddle of a small defect<sup>1</sup> in the septum separating the accessory median, from the left atrial chamber (fig. 1 *D*). Measurements of the outlets of the pulmonary vein made with a calibrated cone, indicated that approximately one tenth of the total pulmonary return could thus enter the left atrium directly.

1. Instances of the opening of either the superior vena cava or the right pulmonary veins astride of a septal defect which gives the entering blood access to either atrium have been reported by: Chiari (*Einmündung der rechtsseitigen Pulmonalvenen im rechten Vorhof*. *Defecte im Septum Atriorum*, *Jahrb. f. Kin-*

Superiorly, the apex of the wedge-shaped accessory chamber did not extend all the way to the cephaloventral wall of the atria (fig. 1 *B* and *C*). There was thus a place in which the right and left atrial chambers were not separated from each other by the accessory median chamber. In this region there was an oval orifice in the right-hand septum, guarded only by a loose flap of the left-hand septum (fig. 1 *C*) which would permit blood to pass freely from the right atrium to the left. Although this orifice was perhaps a little farther from the inferior caval opening than was normal, its relations clearly placed it as the foramen ovale (fig. 2).

## COMMENT

The astonishing circulatory paths presented by this heart are diagrammatically summarized in figure 3. Nine tenths of the blood returning from the lungs entered the accessory median atrium, which was virtually cut off from the left side of the heart. From this median chamber, the blood passed through a large septal defect (117 sq. mm.) into the right atrium. Thence it was distributed between the enlarged right ventricle, which must have received the major share, and the left atrium, which could receive mixed blood through an open foramen ovale (functional orifice 30.2 sq. mm.). The mixed blood thus entering the left atrium was enriched by the direct entrance of but a small fraction (approximately one tenth) of the blood returning from the lungs. This almost negligible contribution of fully oxygenated blood was delivered by the right superior pulmonary vein which opened astride of a small hole (3.2 sq. mm.) in the left septum near the foramen ovale. The enlarged pulmonary artery contributed to the deficient volume of the systemic circulation over an open ductus arteriosus, but the mixed blood thus brought into the aorta could have been of small help in relieving the oxygen deficiency in the systemic circuit.

The enlargement of the right side of the heart may be attributed to the excess of blood entering on that side; for the right atrium received not only the normal caval return, but also, by way of the septal defect, most of the blood that should have gone to the left atrium. The enlarged right ventricle and the oversized pulmonary artery would naturally follow. The same conditions which increased the volume of blood received by the right side of the heart entailed a corresponding decrease in the blood volume received by the left side of the heart.

derh. **15**:319, 1880); Geddes (Abnormal Superior Vena Cava, *Anat. Anz.* **41**:449, 1912); Hepburn (Double Superior Vena Cava, Right Pulmonary Veins Opening into Right Auricle and a Special Inter-Auricular Foramen, *J. Anat. & Physiol.* **21**:438, 1887); Ingalls (Vena Cava Superior Receiving Two Upper Right Pulmonary Veins and Opening into Both Atria, *Bull. Johns Hopkins Hosp.* **18**:136, 1907); Wagstaffe (Two Cases of Free Communication Between the Auricles by Deficiency of the Upper Part of the Septum Auriculorum, *Tr. Path. Soc. London* **19**:96, 1868). Such cases are of incidental interest in connection with the unusual mode of entrance of the right superior pulmonary veins in the case under consideration.



The small capacity of the left atrium and ventricle, the underdeveloped ventricular musculature and the undersized aorta were the inevitable consequences.

The inefficiency of this cardiovascular mechanism which was constantly sending to the lungs blood already partially saturated with

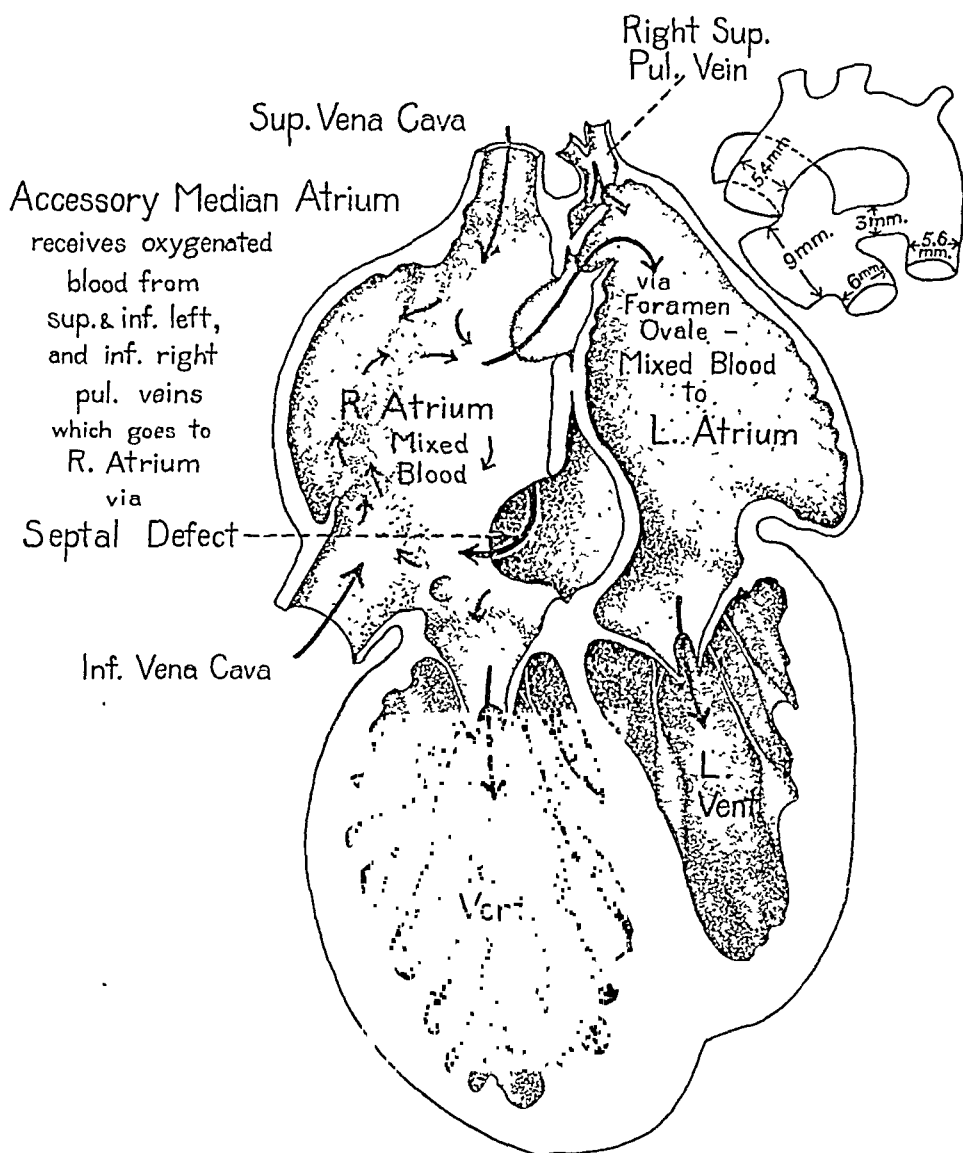


Fig. 3.—Schematic diagram of the dorsal half of the heart laid open to show the course of the circulation through the three atrial chambers. The relative sizes of aorta, pulmonary artery and ductus arteriosus are indicated by the sketch inserted in the upper right hand corner of the illustration.

oxygen, and to the systemic circulation blood deficient in oxygen and overloaded with carbon dioxide was clearly indicated by the rapid gasping respiration and the marked cyanosis. The surprising thing is not that such a mechanism failed to support life, but that the infant with it was able to survive for as long as three months.

## EMBRYOLOGIC INTERPRETATION

We cannot rule out the possibility that there may be certain types of congenital defects that are of purely hereditary origin. The high incidence of structural variations in offspring produced following the irradiation of parental gonads (Little and Bagg;<sup>2</sup> Muller<sup>3</sup>) indicates that disturbances in the gametes themselves may determine certain structural anomalies before intra-uterine life has commenced. But it seems highly improbable that all or even most anomalies are thus irrevocably fixed at the time of fertilization.

Increasing evidence is being accumulated that disturbances in the living conditions of a growing embryo can and do produce developmental distortions (Mall,<sup>4</sup> Mall and Meyer<sup>5</sup>). Furthermore, it is known that the same disturbing factor, applied under experimental control at different stages of development, produces not the same but different anomalies (Stockard<sup>6</sup>). This seems to mean that the nature of the distortion so produced depends on what developmental happenings were in a rapidly progressing and, therefore, sensitive and readily modifiable stage (Hyman<sup>7</sup>) when the disturbance in the embryo's living conditions occurred, rather than on the nature of the disturbance itself. It seems not impossible that further experimental work along these lines may lead to the recognition of disturbing factors in intra-uterine environment that can be controlled. It may, therefore, become of more than academic interest to know at precisely what stage of development a given type of malformation had its incipience.

In spite of the extraordinary functional picture presented by the heart under consideration, the nature of the embryologic distortion which must have produced it does not appear so obscure as one might, at first glance, believe. Normally, there are formed, in the partitioning

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2. Little, C. C., and Bagg, H. J.: The Occurrence of Four Inheritable Morphological Variations in Mice and Their Possible Relation to Treatment with X-Rays, *J. Exper. Zool.* **41**:45, 1924.

3. Muller, H. J.: The Production of Mutations by X-Rays, *Proc. Nat. Acad. Sc.* **14**:714, 1928.

4. Mall, F. P.: A Study of the Causes Underlying the Origin of Human Monsters, *J. Morphol.* **19**:1, 1908; On the Frequency of Localized Anomalies in Human Embryos and Infants at Birth, *Am. J. Anat.* **22**:49, 1917.

5. Mall, F. P., and Meyer, A. W.: Studies on Abortuses: A Survey of Pathologic Ova in the Carnegie Embryological Collection. *Contrib. Embryol.* **12**:1, 1921.

6. Stockard, C. R.: Developmental Rate and Structural Expression: An Experimental Study of Twins, "Double Monsters" and Single Deformities, and the Interaction Among Embryonic Organs During Their Origin and Development, *Am. J. Anat.* **28**:115, 1921.

7. Hyman, L. H.: The Metabolic Gradients of Vertebrate Embryos: IV. The Heart, *Biol. Bull.* **52**:39, 1927.

of the originally common atrial chamber, two interatrial septums. Following the terminology of Born<sup>8</sup> one commonly designates these as interatrial septum primum (or septum I) and interatrial septum secundum (septum II). Septum primum has normally made its appearance as a crescentic partition on the cephalodorsal wall of the primitive common atrium by the end of the first month of development. (It is well formed in 4 mm. embryos.) By the end of the second month, septum primum meets and fuses with the atrioventricular canal cushions which divide the primitive atrioventricular canal into right and left channels. Just before this fusion occurs, it seems as if the two atria were destined to be prematurely separated, leaving the left side of the heart with no entering blood save an insignificant trickle from the

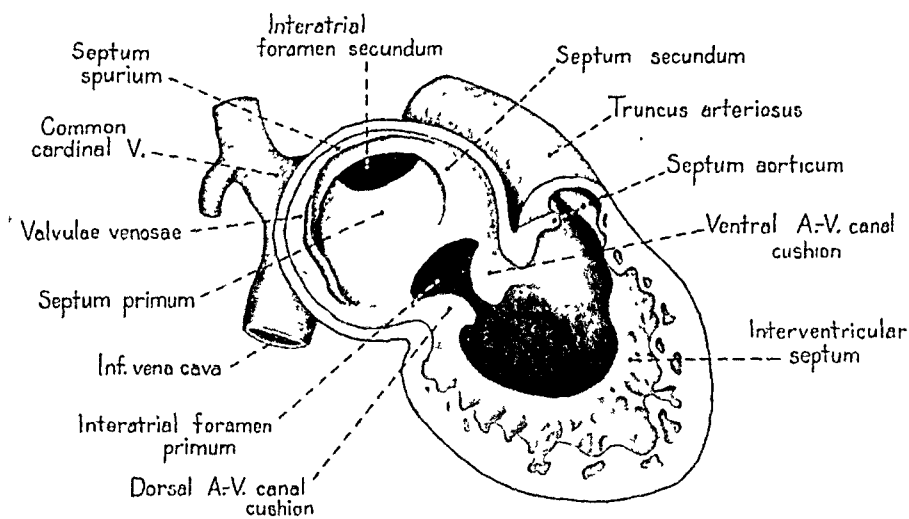


Fig. 4.—Drawing illustrating the relations of septum primum and septum secundum in the embryonic heart. (Semischematic combined illustration, in part from the figures of Born and Tandler and in part from reconstructions and dissections by one of us.) If one imagines septum primum starting to form abnormally far to the left, so that it grows all the way to the atrioventricular canal cushions without becoming fused with septum secundum, the condition exhibited by the abnormal heart under consideration would be established (compare with fig. 2).

developing pulmonary veins. But at this critical time, a secondary opening appears in septum primum. This secondary opening (the ostium secundum of Born), formed by the local disintegration of septum primum near its point of origin from the cephalodorsal wall of the atrium, permits continued access of blood to the left atrium (fig. 4).

Meanwhile a second interatrial partition has started to form immediately to the right of septum primum. Like the septum primum when

8. Born, G.: Beiträge zur Entwicklungsgeschichte des Säugethierherzens, Arch. f. mikr. Anat. **33**:284, 1889.

it first appeared, the newly formed septum secundum is of crescentic shape with its concavity directed toward the atrioventricular canal (fig. 4). The tips of the crescent, however, instead of reaching all the way to the atrioventricular canal, blend with septum primum. Thus, if septum primum is defective and fails to close off the original interatrial communication, septum secundum does not complete the partition, and there remains a characteristically located septal defect (fig. 5). The fact that it is septum primum rather than septum secundum that forms the portion of the definitive interatrial septum near the orifices of the atrioventricular canal has, if recognized at all, received little emphasis. It seems to us the key at once to defects of the type shown in figure 5, and to the more complex conditions in the heart under discussion.

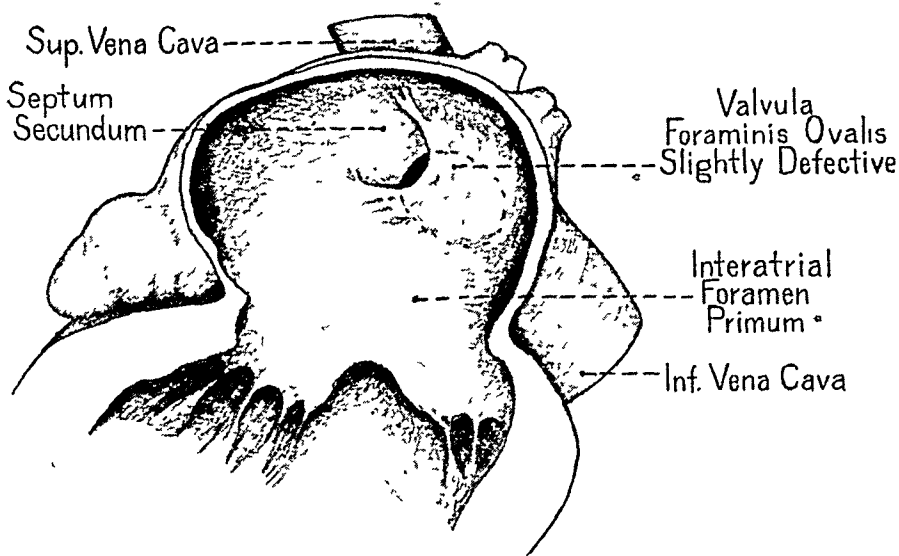


Fig. 5.—Heart showing a large septal defect in the region occupied by the interatrial foramen primum of embryonic life (drawn from specimen no. 264, in the museum of the Pathologisch-anatomisches Institut, Vienna). The case, in a boy, aged 19, was described but not illustrated by Rokitanski (*Die Defecte der Scheidenwände des Herzens*, Vienna, Wilhelm Braumüller, 1875; his case 4). It exemplifies a not uncommon type of interatrial defect of interest in this connection because it shows the way in which septum secundum fails to grow to the atrioventricular canal independently, when there is an arrest in the development of septum primum. In our case, displacement of septum primum so far to the left that septum secundum cannot fuse with it has apparently produced the same results that are encountered when septum secundum lies in the normal relation to an arrested septum primum. In both cases, lacking the lead of septum primum, septum secundum fails to reach the atrioventricular canal cushions. (Compare figs. 2, 4 and 5.)

The extension of septum secundum takes place mainly toward the orifice of the inferior vena cava. Its growing margins bound a rounded opening, the foramen ovale, which becomes reduced in size as development progresses, but which is never obliterated. On the left side of

septum secundum, the remains of septum primum lie as a loose flap covering the foramen ovale and acting as a one-way valve, which is readily pushed aside by blood pressure from the right, but which closes the orifice on pressure from the left. Thus, in the fully formed heart, the interatrial septum is, superiorly, the septum secundum of embryonic stages, while toward the atrioventricular canal, septum primum and septum secundum become fused with each other, septum primum contributing certainly the major portion, if not all, of this part of the definitive septum. Above the fusion, septum primum remains until after birth as an independent flap, the *valvula foraminis ovalis*. After the foramen ovale is anatomically closed, as normally occurs late in the first postnatal year, the *limbus fossae ovalis* still marks the old margin of the embryonic septum secundum. On the left atrial side, close inspection of the septum will show the crescentic line of the old free margin of septum primum where it has become fused to septum secundum.

What originally started the heart under consideration off the normal path that has been briefly outlined, one can only conjecture. The embryologic interpretation of the structures present seems, however, clear. The septum between the accessory median chamber and the left atrium is septum primum. Its free upper margin serving as a *valvula foraminis ovalis* (fig. 1C) and its basal attachment to the atrioventricular canal septum (fig. 3) are absolutely characteristic. It is peculiar only in having its origin from the dorsal atrial wall abnormally far to the left. The septum between the median chamber and the right atrium is septum secundum. The oval foramen, the relations of the *crista terminalis* and those of the caval and coronary valves are all characteristic (figs. 1 and 2). It is abnormal only because of the existence of an opening, located just above the base of the atrioventricular valves and communicating with the accessory median chamber.

A similarly located defect in an otherwise fairly normal heart is shown in figure 5 for comparison. The opening in both cases is in that part of the definitive interatrial septum which we believe to be formed normally by the septum primum. In the heart with but the normal two atria, we would interpret the defect as being due primarily to failure of septum primum to reach the atrioventricular canal partition. Later, when septum secundum fused with septum primum, it did not carry the lower border of the interatrial partition beyond the level at which septum primum was arrested, thus leaving the primary interatrial ostium permanently open. In our case, septum primum has grown all the way down to and fused with the atrioventricular canal cushions, but it was so far displaced to the left at this point that septum secundum could not fuse with it. Thus, although septum primum has completely obliterated the primary interatrial ostium, there remains a gap at the

base of the interatrial septum where defects due to failure to close ostium primum ordinarily appear. This condition would seem to offer unusually good confirmation of the view that the definitive interatrial septum in this region is formed primarily by septum primum rather than by septum secundum, for there is in this case a septal defect due not to deficient growth of either septum I or septum II, but to the accident which separated the two in a region where they normally complement each other.

Looking at this curious heart from another standpoint may help to make its interpretation clear. If one visualizes septum primum as retaining ventrally the relations shown in the section diagrams of figure 1, but having its dorsal attachment swung over against septum secundum one has practically a normal heart. The accessory median chamber would be obliterated, the pulmonary veins would empty as they should into the left atrium, and the interauricular septal opening would be closed.

#### RELATED CASES

Although, as was stated in the introduction, we could find no record of a heart presenting the curious structural and functional conditions here described, there are several cases reported in the literature that involved a similar developmental distortion. The one that seems to come closest to our own case was described by Hosch.<sup>9</sup> His case was that of a 25 day old infant who presented a closely similar clinical picture and fundamentally the same embryologic distortion. There was in Hosch's case, however, an opening through septum primum directly from the accessory median chamber into the left atrium, and consequently there was not the extraordinary circuitous routing of the blood returned from the lungs to the median atrium that was so striking a feature in our case.

Another heart of the same general type, from an infant who lived but a short time, was reported by Stoeber.<sup>10</sup> The accessory median atrium in his case, however, seems to have been a small pocket receiving only the veins from the lower lobes of the lungs. The veins from the upper lobes of both lungs opened into the right atrium, which was in communication with the left, over a widely patent foramen ovale.

Cases involving a similar but less complete division of the primary atrium into three chambers were reported by: Borst<sup>11</sup> (in a woman

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9. Hosch, P. H.: Zur Lehre der Missbildungen des linken Vorhofs: II. Ein Herz mit linken Doppelvorhof, Frankfurt. Ztschr. f. Path. **1**:563, 1907.

10. Stoeber, H.: Ein weiter Fall von Cor triatriatum mit eigenartiggegrenzter Mündung der Lungenvenen, Virchows Arch. f. path. Anat. **193**:252, 1908.

11. Borst, M.: Ein cor triatriatum, Verhandl. d. deutsch. path. Gesellsch. **8**:178, 1905.

aged 38); Church<sup>12</sup> (in a woman aged 38, mother of four children); Potter and Ranson<sup>13</sup> (in an "adult" male negro); and William and Abrikossoff<sup>14</sup> (in a boy aged 11).<sup>2</sup> With the exception of Church, whose paper antedates the fundamental work of Born<sup>8</sup> and Tandler<sup>15</sup> on which the present conception of heart development is based, these authorities are in fair agreement regarding the accessory septum as a displaced septum primum, although their conjectures as to the manner and cause of its displacement vary considerably.

Other cases involving what was described as a partial subdivision of the left atrium by a "fibrous band" have been reported by: Griffith<sup>16</sup> (two cases), Fowler<sup>17</sup> and Martin.<sup>18</sup> Probably also Preisz'<sup>19</sup> cases 13 and 14 should be included in this group.<sup>20</sup> It is difficult to be certain without an opportunity of studying the actual specimens, but all these cases of a fibrous band across the left atrium would seem to be instances of a septum primum displaced to the left. If this interpretation is correct, these hearts belong in the same general category embryologically as the true triatrial hearts, for they exhibit the same malposition of the same septum, differing only in that the septum is meager in extent.

Clinically, of course, the cases with a mere fibrous band presented a picture different from the cases in which there was an almost completely isolated accessory chamber. They gave little or no manifestation of cardiac disturbance, and the existence of any malformation was

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12. Church, W. S.: Congenital Malformation of Heart: Abnormal Septum in Left Auricle, *Tr. Path. Soc. London* **19**:188, 1868.

13. Potter, P., and Ranson, S. W.: A Heart Presenting a Septum Across the Left Auricle, *J. Anat. & Physiol.* **39**:69, 1904.

14. William, N., and Abrikossoff, A.: Ein Herz mit linkem Doppelvorhofe, *Virchows Arch. f. path. Anat.* **203**:404, 1911.

15. Tandler, J.: The Development of the Heart, in Keibel and Mall: *Manual of Embryology*, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 534.

16. Griffith, T. W.: Heart with a Fibro-Muscular Band Passing Across the Cavity of the Left Auricle, *J. Anat. & Physiol.*, 1896, vol. 30, *Proceedings*, p. 6; Note on a Second Case of a Division of the Cavity of the Auricles into Two Compartments by a Fibrous Band, *ibid.* **37**:255, 1903. \*

17. Fowler, J. K.: Membranous Band in the Left Auricle, *Tr. Path. Soc. London* **33**:77, 1882.

18. Martin, S.: A Heart with Left Auricle Divided by a Septum, *J. Anat. & Physiol.*, 1899, vol. 33, *Proceedings*, p. 31.

19. Preisz, H.: Beiträge zur Lehre von den angeborenen Hertzanomalien, *Beitr. z. path. Anat. u. z. allg. Path.* **7**:245, 1890.

20. The case of triatrial heart reported by Sternberg (*Beiträge zur Herzpathologie, Verhandl. d. XIV deutsche path. Gesellsch.* 1913, p. 253) appears to belong in a totally different category. He described it as having a double right atrium. From his description it would seem that the anomaly might be due rather to persistence of a strongly developed septum spurium than to malposition of septum secundum as he suggests. In any event, the septum primum was not involved as was the case with the heart under consideration.

unsuspected till discovered at the autopsy table or in the dissecting room. Taken as a group, the cases in which the septum is strongly developed show an increase in the severity of symptoms and a decreased tenure of life proportional to the completeness with which the displaced septum primum shuts off from the left atrium, the blood returned from the lungs to the median atrium.



# THE FORMATION OF HYALIN IN THE OVARIES\*

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Hyaline substances in the ovary are common. Most of this hyalin appears in the form of bulky hyaline masses which are usually interpreted as results of the involution of lutein bodies. Other smaller hyaline bodies are derived from the involution of atretic ovarian follicles. In reviewing the literature, we find that no other form of hyalinization is mentioned, and the foregoing interpretation of the hyaline bodies is given also by all the textbooks of pathology.

Boeshagen<sup>1</sup> distinguished various kinds of hyalin and mentioned the following four types as the most important:

1. The corpus atreticum. This is a small body, round or oval of shape. Its center consists of fibrous or slightly myxomatous tissue, while the periphery appears sometimes as a homogeneous hyaline seam.

2. The corpus fibrosum. This is larger. It consists of irregularly outlined and more or less thoroughly hyalinized fibrous tissue. There is no hyaline seam in the periphery.

3. The corpus candicans. This is usually elongated and gyrated. Its substance is homogeneous, with the exception that in the center it reveals a small area of fibrillar structure.

4. The corpus albicans. This is much more powerfully developed and consists also mainly of hyalin. There is some fibrillar scar tissue in the center which, although more extensive than in the corpus candicans, is still scanty compared with the surrounding hyaline masses.

Transitions between these four major types are frequent. Boeshagen's interpretation is indicated already by his nomenclature. He assumed that the corpus atreticum develops from degenerating ovarian follicles, whereas the other three types derive from lutein bodies and develop according to the part in which fibrosis or hyalinization occurs in the process of involution.

Observations made on a large number of ovaries which were removed surgically or obtained at autopsy gave us the impression that there are many more sources of hyaline formation. In order to prove this point, systematic studies were made on a series of sixty ovaries.

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\* Submitted for publication, June 19, 1929.

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1. Boeshagen: *Ztschr. f. Gynäk.* **53**:323, 1904.

Almost every ovary in this series showed the presence of more or less extensive hyalinization; in four only, no hyalin was found. The age of the patient seems to bear no relation to the presence or the extent of the hyalinization. As a matter of fact, large hyaline bodies were present in the ovaries of some of our youngest patients, while there were smaller ones in some of the older patients. The ages of the patients varied from 19 to 53 years.

In studying the regressive changes of lutein bodies, we were impressed by the early invasion of their central portion by connective tissue cells. The proliferation of the latter organizes the hematoma and the necrotic area which are formed in the menstrual body and later also in the lutein body of pregnancy. The peripheral area of the lutein body survives longer, but its final degeneration is inevitable, and the lutein tissue is also replaced by connective tissue. Hyalinization of such scars is a regular feature, but it never goes so far as totally to obscure the fibrillar structure. Boeshagen's description of the corpora fibrosum, candicans and albicans applies fairly well to these bodies, although it is difficult to explain according to his conception why the larger peripheral areas of the corpus albicans and the corpus candicans become so homogeneous. The typical product of the involution of the lutein body is the corpus fibrosum, which is characterized by its irregular elongated, or often stripelike, shape. Another feature of the corpus fibrosum is the presence of pigment, notably hemosiderin, which is seldom missing in its central portion (fig. 1). The pigment is either extracellular or phagocytosed by large cells.

There is no difficulty in recognizing the origin of the corpus atreticum. Rabl, Cohn<sup>2</sup> and particularly Seitz<sup>3</sup> have called attention to regressive changes of the ovarian follicles which do not mature and which degenerate without producing lutein bodies (fig. 2). Still it seems that the cells of the follicular capsule (theca cells) store lipoids and assume a shape resembling that of the lutein cells. They have been spoken of as theca lutein cells and are supposed to proliferate extensively in later pregnancy. Their proliferation, however, has been observed also without pregnancy; probably in connection with menstrual changes. The later fate of these cells has been much discussed. Miller<sup>4</sup> and Wolz<sup>5</sup> held that they degenerate and elicit thereby further changes. The origin of these so-called theca lutein cells has also been questioned. Besides their origin from perifollicular theca cells, an origin from the cells of the ovarian stroma has been claimed for them, particularly by Benthin.<sup>6</sup> He also claimed that these cells, after dis-

2. Cohn: Arch. f. Gynäk. **77**:367, 1909.

3. Seitz: Zentralbl. f. Gynäk. **29**:257, 1905.

4. Miller: Arch. f. Gynäk. **91**:263, 1910.

5. Wolz: Arch. f. Gynäk. **97**:131, 1912.

6. Benthin: Arch. f. Gynäk. **91**:498, 1910.

posing of the stored up lipoids, are capable of reverting to their original type, assuming the shape of ordinary stroma cells. According to this conception, the so-called vegetation of the lutein cell represents merely a peculiar functional stage of the ordinary ovarian stroma. Benthin's interpretation has been opposed by various observers, especially by Seitz,<sup>3</sup> who claimed that it is easy to show on serial sections a connection between apparently independent groups of lutein cells and atretic follicles. But even Seitz conceded his failure to demonstrate this

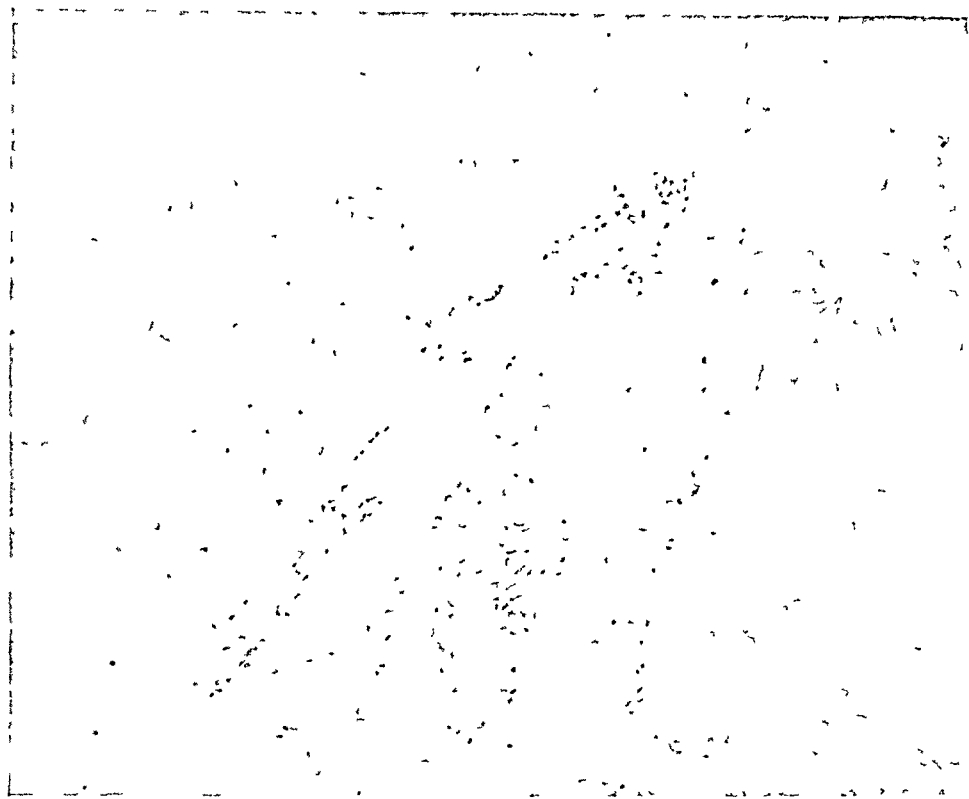


Fig. 1.—Involution of lutein body; hyalin in the periphery; fibrotic center, deposit of hemosiderin.

connection in a good many cases. Our own experience has shown that foci of lipoidal cells are often independent from atretic follicles. They occur just as frequently in the deeper medullary portion of the ovary, where follicles are not met with. Transitional forms between ordinary ovarian stroma cells and large lipid-storing cells are readily observed. We believe that these cells should not be spoken of as lutein cells, since they are different both as to morphology and as to histogenesis from the cells of the lutein body.

The real lutein cell is dense of structure; its cytoplasm is definitely eosinophile, with the exception of a few scattered cells conspicuous for their basophile cell body. Fat-storing cells of the ovarian stroma, on

the other hand, remain practically unstained if hematoxylin eosin is used. Their cytoplasm is foamy and encloses lipoid droplets which are more soluble in alcohol than those of the real lutein cells. The shape of the nuclei is also different. The nucleus of the lutein cell is comparatively large and round and reveals an orderly structure of the chromatin. The nucleus of the stroma cell, on the other hand, is smaller and usually pyknotic. This seems to suffice for distinguishing sharply between these two types of cells. Hence, we shall refer to lipoid-

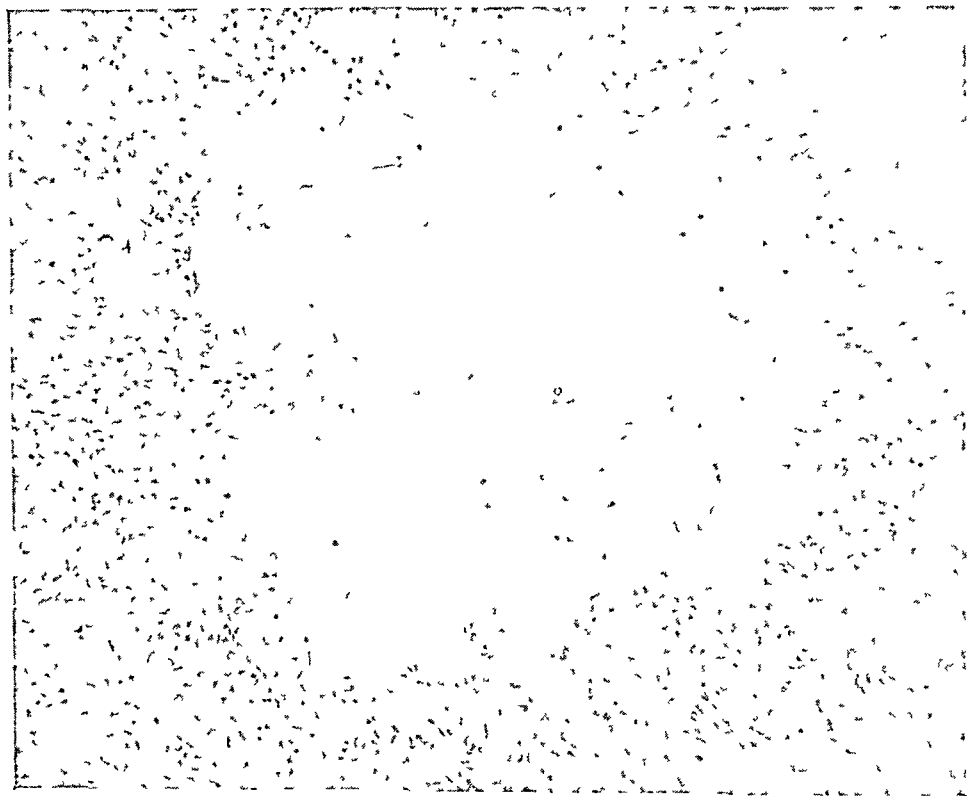


Fig 2—Myxomatous focus with hyaline seam, atretic follicle.

storing cells of the ovarian stroma as "lipoidal cells" in contradistinction to the real lutein cells described.

Regressive changes of the lipoidal cells are recognized by the disappearance of the lipoidal material and by subsequent alteration of the cytoplasm. The disappearance of the lipoids is not always followed by injury or death of the cell. The former lipid cell appears thereafter as an ordinary connective tissue cell or assumes stellate shape and resembles the cells of myxomatous connective tissue. This is apparently due to a collection of fluid in this area. It is in keeping with the fact that the disappearance of fats or lipoids from various tissues is accompanied by a collection of fluid, as, for example, in the cortex of the

suprarenal gland in severe infections (Kutschera-Aichbergen<sup>7</sup>). The myxomatous tissue that forms in the ovary after the resorption of lipoids undergoes sometimes even further changes. Gradual loss of the accumulated fluid transforms the area into plain fibrillar connective tissue in which the cells are small and scanty.

The regressive changes of the lipid cells, however, are frequently associated with necrotic features. The cytoplasm of the cells becomes homogeneous simultaneously with the resorption of the lipoids. Exudation of an albuminous substance between the cells is concomitant. First,

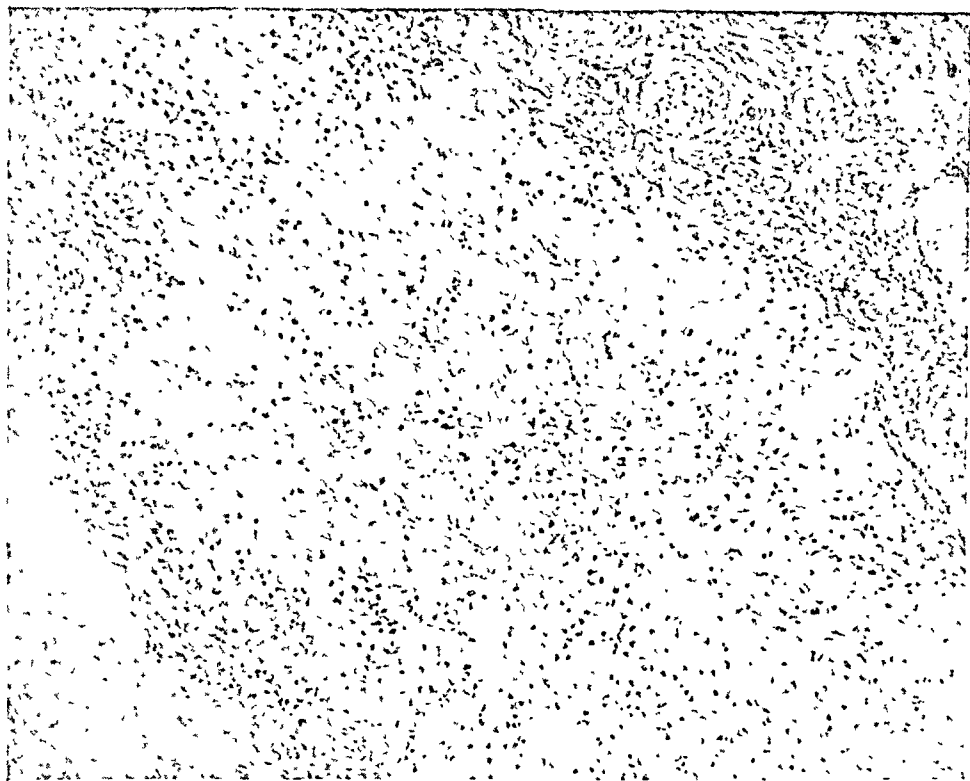


Fig. 3.—Hyaline degeneration of lipoidal cells in ovarian stroma.

the outlines of the cell bodies disappear, and the nuclei succumb to chromatolysis. Finally, the whole area is transformed into a hyaline mass.

The sources of hyalin in the ovary are not exhausted by the regressive changes of lutein bodies and the vegetations of lipid cells, or by those of the atretic follicles. Independently from such structures, hyaline material is directly formed in the ovarian stroma. The final product of hyalinization in the ovarian stroma is not easily distinguished from hyalin that derives from any of the sources mentioned. The early stages, however, are characteristic. At the onset, minute deposits

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7. Kutschera-Aichbergen: *Verhandl. d. deutsch. path. Gesellsch.* **20**:133, 1925.

of hyalin of annular shape surround the single stroma cell. While this ring of hyalin becomes more massive, the stroma cell shows evidence of progressing atrophy with the result that a small spindle-shaped nucleus is left in the center of a lump of hyalin. Isolated hyaline rings of this type are rare. Hyalin develops usually about a whole group of cells. Many of these rings coalesce and form wavy, garland-shaped structures (fig. 4). The process resembles closely hyalinization in a lymph node or a deposit of amyloid. The reaction of the ovarian stroma cells to the presence of hyalin is similar; atrophy of cells is followed

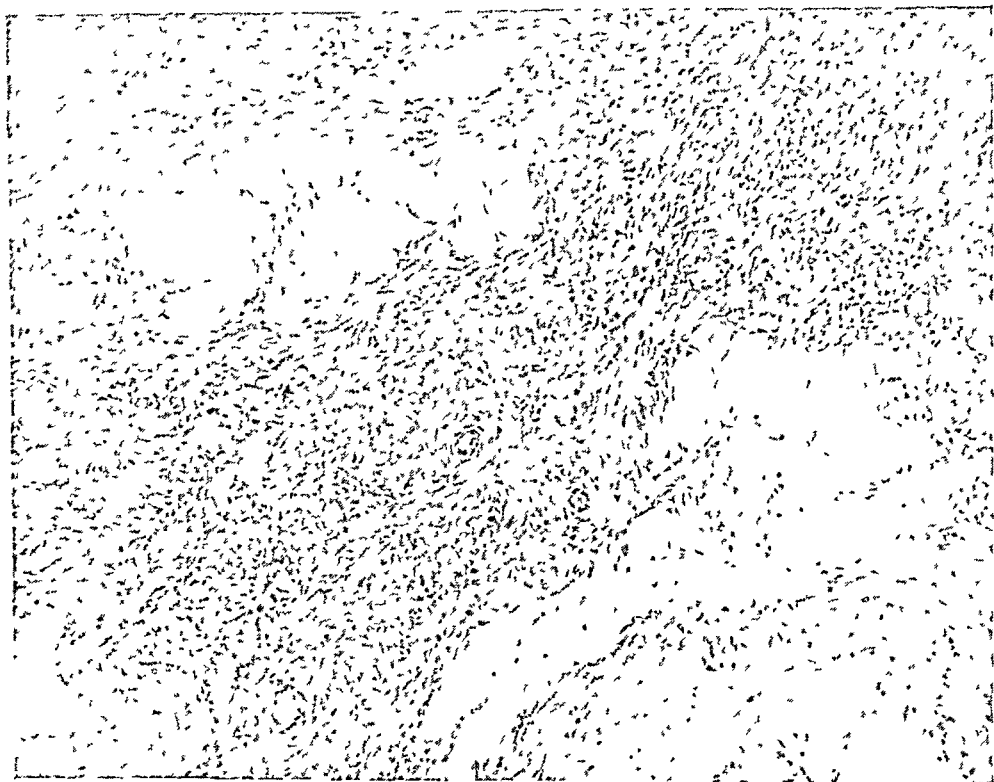


Fig. 4.—Formation of hyalin in the ovarian stroma.

sooner or later by complete disappearance of the nuclei; finally the hyalin coalesces to form solid masses of gyrated shape (fig. 5).

Hyalinization of the ovarian stroma of the type described occurs both in the cortex of the ovary and in the stroma of the medulla. These deposits of hyalin are sometimes insignificant, but they may involve also a large portion of the ovary. Careful review of our material leads us to the conclusion that most of the hyaline bodies and particularly the large ones derive from direct changes in the ovarian stroma.

Another group of hyaline changes includes those developing in the walls of blood vessels. Hyalin is frequently deposited in the wall of the small and medium-sized arteries or veins. Most of this hyalin occurs in the media, but deposits are found also in the intima and the

adventitia. The specific elements of the musculature disappear with increasing hyalinization, while the lumen of the vessel is often narrowed down considerably. Complete obliteration of the blood vessel is the final stage. This is brought about by homogeneization of the vessel wall and coalescence of its structures into a solid hyaline, disklike body. Vessels with such extensive hyalinization usually occur in densely packed groups (fig. 6). If the adventitia is also involved, as often happens, some of these vessels fuse, forming a large hyaline body. This body is oval and elongated, and its gyration resembles that of the hyaline

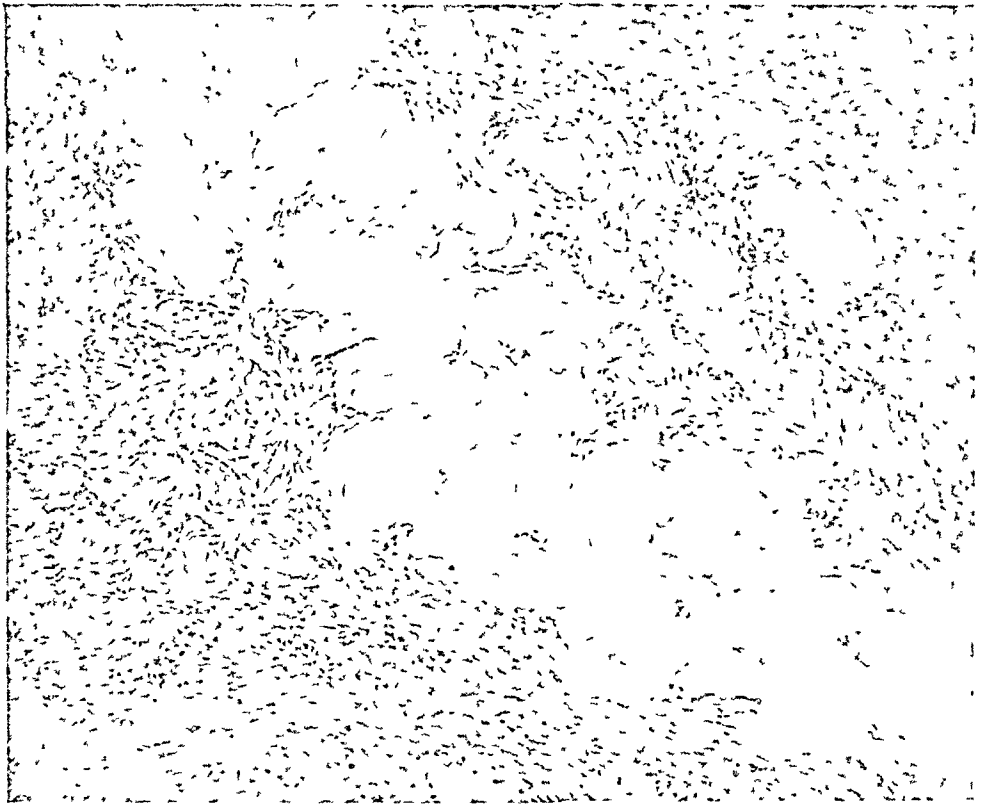


Fig. 5.—Coalescing hyaline garlands

structures formed within the ovarian stroma. It is almost impossible to distinguish these late stages of vascular degeneration from other products of hyalinization. Residua of the original structure persist sometimes and reveal the histogenesis. Earlier stages of such vascular changes in the vicinity of hyaline bodies can be considered as further circumstantial evidence.

Severe impairment of the ovarian blood vessels, particularly in the medulla, has been discussed previously by several authors (Sohma,<sup>8</sup> Miller,<sup>4</sup> Clark<sup>9</sup>). Their interpretation is that the lesion develops in

8 Sohma: *Arch. f. Gynak* **84**:377, 1908.

9. Clark: *Surg. Gynec. Obst.* **13**:99, 1911.

connection with disturbances during pregnancy. Other authors thought that these changes might result from the strain to which the ovarian vessels are subjected during menstruation. Neither of these theories has been sufficiently substantiated. Yet it is fair to say that the vascular changes are not in proportion to the age of the person and cannot be explained simply as products of senile involution.

#### SUMMARY AND COMMENT

We have distinguished in the foregoing description between various types of hyalinization in the ovary. Our differentiation is based on the

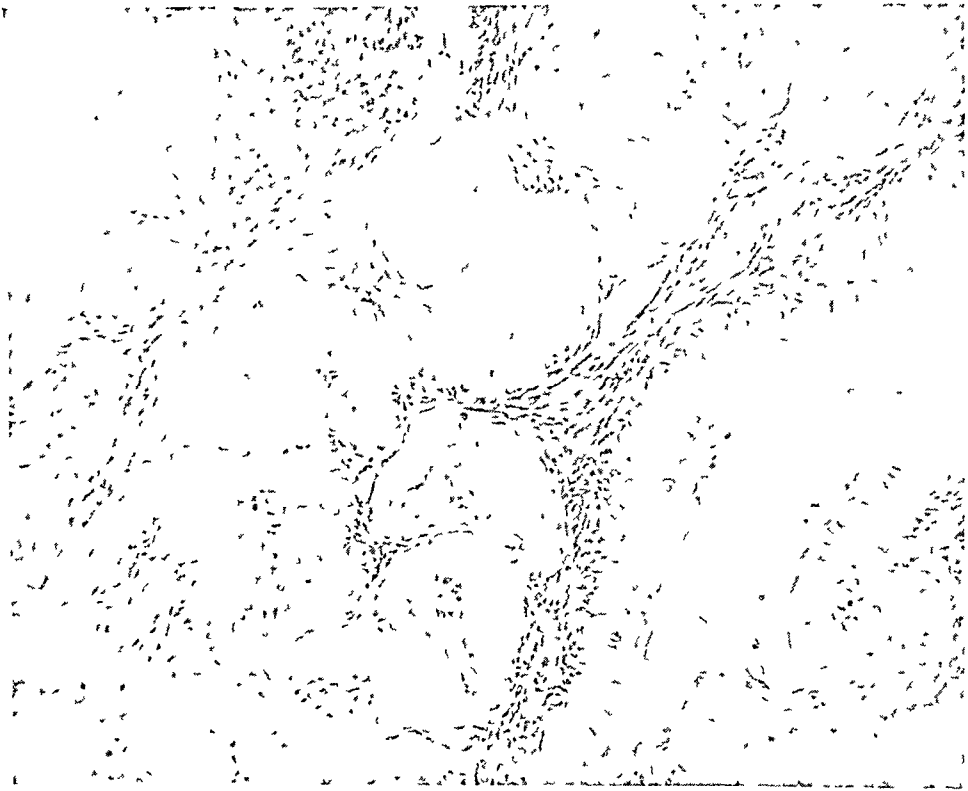


Fig. 6—Hyalinization of ovarian blood vessels.

morphologic appearance of the hyaline bodies. Yet it also takes into consideration their histogenesis as brought out by comparing earlier and later stages. Summarizing briefly, we may state that there are five types of hyaline bodies in the ovary. The first derives from lutein bodies and is fairly well characterized by its scarring center and the presence of hemosiderin. The second type is a small hyaline body developing from an atretic follicle through degeneration of theca lipid cells. The third type develops from lipid cells that were formed in the ovarian stroma independently from any follicle. Degeneration of such lipid cells yields a colorful picture as myxomatous or plain



fibrous areas intermingle. The fourth type develops directly within the specific ovarian stroma and represents a primary lesion of the stroma cells. The fifth group is the result of changes to which the ovarian blood vessels were subjected.

We have to emphasize that in their fully developed stage, all the different types of hyaline bodies may look so similar that histogenetic differentiation is not possible. Differential diagnosis can be made only in the early stages. But even then difficulties may arise in that several types occur simultaneously and combine to form puzzling structures. The most common combination is a deposit of hyalin in the ovarian stroma adjacent to a hyalinized lutein body. It is not rare to find vegetations of lipoidal cells near, or surrounding, a comparatively recently involuted lutein body. Coalescence of the two different structures forms a large body, the core of which represents the residua of the lutein body, and the periphery, the degenerated lipoidal cells. The distribution of the hyalin may be annular or crescent-like. Hyalinized blood vessels may also participate in the formation of a homogeneous marginal zone about an involuted lutein body. Hyalinized blood vessels, however, coalesce more frequently with masses of hyalin formed directly in the ovarian stroma.

We do not know the real significance of hyalinization in the ovary. We could not by comparing establish any definite relationship between the age of the patient and the extent of the changes. The presence of extensive lesions in young persons seemed to prove that hyalinization in the ovary is not connected with senile involution. We tried to determine in our surgical cases whether any coincidence obtained between ovarian hyalinization and disturbances of menstruation. We were unable to find any convincing evidence of this. However, most of our material was obtained from patients on whom operations had been performed for some disturbance of the genital sphere. Therefore, this material does not seem to be suitable for deciding on the relationship of ovarian hyalinization to clinical symptoms. It would be necessary to study an equal number of ovaries from patients who were without any disturbance of the genital organs.

#### CONCLUSIONS

Hyalinization of the ovary was studied in sixty ovaries. Five types of hyaline bodies were described. They derive from lutein bodies, from atretic follicles, from lipoidal cells of the ovarian stroma, from ordinary stroma cells and from blood vessels, respectively. The histogenesis of a hyaline body can be distinguished only in the early stage of its formation. Combination forms are common.

The clinical significance of ovarian hyalinization requires further comparative studies.

# HEMANGIOBLASTOMA OF THE CEREBELLUM WITH CYST FORMATION (LINDAU'S DISEASE)

REPORT OF A CASE \*

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Cysts comprise about 10 per cent of all cerebellar tumors. It has long been recognized that some of them arise by cystic degeneration of gliomas. The remainder are grouped as nonneoplastic or simple cysts. It was only three years ago, in 1926, that Lindau<sup>1</sup> expounded the origin of many of these so-called simple cysts from small hemangiomas which can be readily found by close inspection of the wall of the cyst. He indicated the heredofamilial character of hemangiomatous cysts, and pointed out also their frequent association with angiomatosis of the retina (von Hippel's disease) or with other visceral tumors. Cushing and Bailey<sup>2</sup> brought his work closer to date, and lent to it special staining analyses. Davidoff<sup>3</sup> recently reported a case of this newly established syndrome.

Altogether, less than sixty cerebellar hemangiomas with cyst formation and companion tumor have been described.<sup>4</sup> Postmortem examination disclosed another one to me. The relatively recent establishment of the syndrome, its infrequency and an unusual feature in my case make the latter worthy of being reported.

## REPORT OF CASE

*Clinical History.*—A male mulatto, about 50 years old, entered the Cook County Hospital. He was apparently well until three months before entrance when he became rapidly weak in the right side of the body and the right arm began to tremble. He managed to carry on for two months longer; then mental deteriora-

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\* Submitted for publication, July 3, 1929.

\* From the Department of Pathology of the Cook County Hospital.

1. Lindau, Arvid: Studien über Kleinhirncysten: Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, suppl. no. 1, pp. 1-128.

2. Cushing, H., and Bailey, P.: Tumors of the Brain Arising from Its Blood Vessels, Springfield, Ill., Charles C. Thomas.

3. Davidoff, L. M.: Hemangioblastoma of the Cerebellum (Lindau), Am. J. Path. 5:141 (March) 1929.

4. After our paper was submitted for publication, an article appeared by Sargent and Greenfield (Hemangiomatous Cysts of the Cerebellum, Brit. J. Surg. 17:84 [July] 1929), reporting a collection of nine cerebellar cysts. In seven of these, angiomas were found. In several cases, a severe trauma to the head was associated. The authors suggest that the trauma may have started the formation of a cyst in a patient who already had an angioma of the cerebellum.

tion set in. It progressed so rapidly that within a month he was practically vegetative. Such was his apathy that from time to time he had to be fed by means of a tube until he could collect himself sufficiently to swallow food of his own accord.

Neurologic examination revealed a spontaneous lateral nystagmus of the eyes, an intention tremor of the right hand and weakness in both lower extremities. There were increased patellar reflexes and an absence of abdominal reflexes. The coordination in both upper extremities was impaired. The Wassermann reactions of the blood and the spinal fluid were negative. Emaciated, volitionless, stuporous, he finally died of a hypostatic bronchopneumonia.

*Postmortem Observations.*—The essential changes were in the brain and the kidney.

**Brain:** The cerebral convolutions were rather deep, and a moderate amount of fluid filled the sulci. The lateral ventricles were but slightly distended with fluid. On the superior aspect of the right hemisphere, the cerebellar tissue over

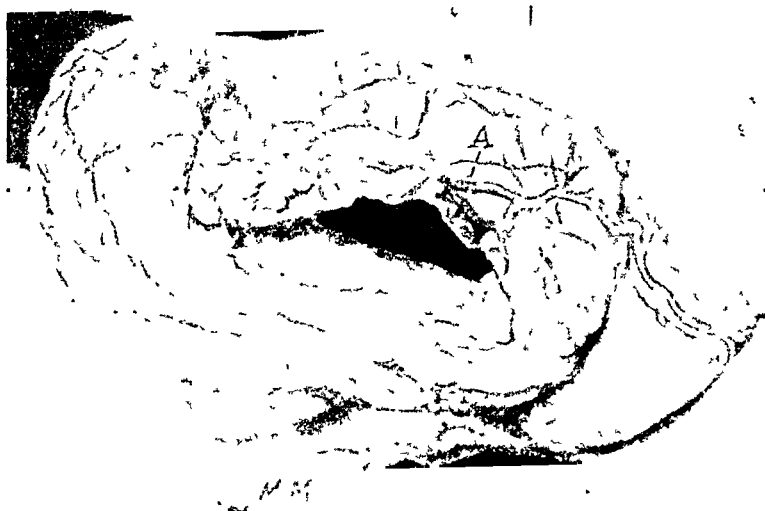


Fig. 1.—A drawing made from the gross specimen, with longitudinal section through the right cerebellar hemisphere, showing the collapsed cyst with its mural tumor (*A*), and its relation to the cortical vessels.

an area 5 by 4 cm. was collapsed to 2 cm. below the surface. In the lateral portion of this depressed area, broadly bridging two of the posterior superior cerebellar vessels, was a deep purple, soft, round mass, the size of a pea, slightly elevated above the surface. Longitudinal section disclosed the right hemisphere, under the depressed area described, to be the site of a large cyst (fig. 1). The cyst attained a size of 4 cm. in the longitudinal, and 3 cm. in the transverse diameter, and 2 cm. in its collapsed height. Its roof was thin; in places, transparent. The mass described was 3.5 cm. thick; it extended through the whole roof of the cyst and bulged into its cavity. On the cut surface, it was reddish purple. The floor of the cyst was lost in broad communication with the fourth ventricle.

Microscopically, the purple nodule on the superior aspect of the cyst was composed of numerous wide, capillary blood spaces, lined by a distinct endothelium (fig. 2). Most of these spaces were filled with blood; some contained only a pale pink, homogeneous, plasmatic material. Fine capillaries could also be dis-

tinguished, with all transitions between them and the larger blood spaces. The intervening, loose fibrillar tissue was occupied by cells which contained each a large, pale, oval or slightly indented nucleus with an ample cytoplasm (fig. 3). Sudan III stain revealed these cells to be filled with lipid. There were also single round cells with deeply stained nuclei and homogeneous cytoplasm. The rest of the wall of the cyst was composed of cerebellar tissue which formed a lining layer, rich in glia, and which continued for but a short distance over the inner aspect of the angiomatous area.

**Kidney:** A 5 mm. white nodule at the corticomedullary line was seen microscopically to be composed of long, narrow and branched tubules lined by irregular cuboidal epithelium with rather pale, round or oval nuclei (fig. 4). The tubules were separated from one another by thin septums, and were divided



Fig. 2.—Low power view of the hemangioma in the roof of the cyst with the adjacent cerebellar tissue lining the rest of the cyst wall;  $\times 28$ .

into groups by thicker strands of fibrillar connective tissue. The nodule was sharply circumscribed but not encapsulated, and a few of its tubules were found outside among the normal ones.

**Pathologic Diagnosis.**—The pathologic diagnosis was: hemangioblastoma of the right cerebellar hemisphere, with cyst formation, the latter communicating with the fourth ventricle (Lindau's disease); adenoma of the kidney; confluent bronchopneumonia of the left lower lobe; edema and hyperemia of the lungs; atrophy and inflammatory softening of the spleen; brown atrophy and cloudy swelling of the myocardium and liver; cloudy swelling and passive congestion of the kidneys, and healed tuberculous primary nodule in the right lower pulmonary lobe.

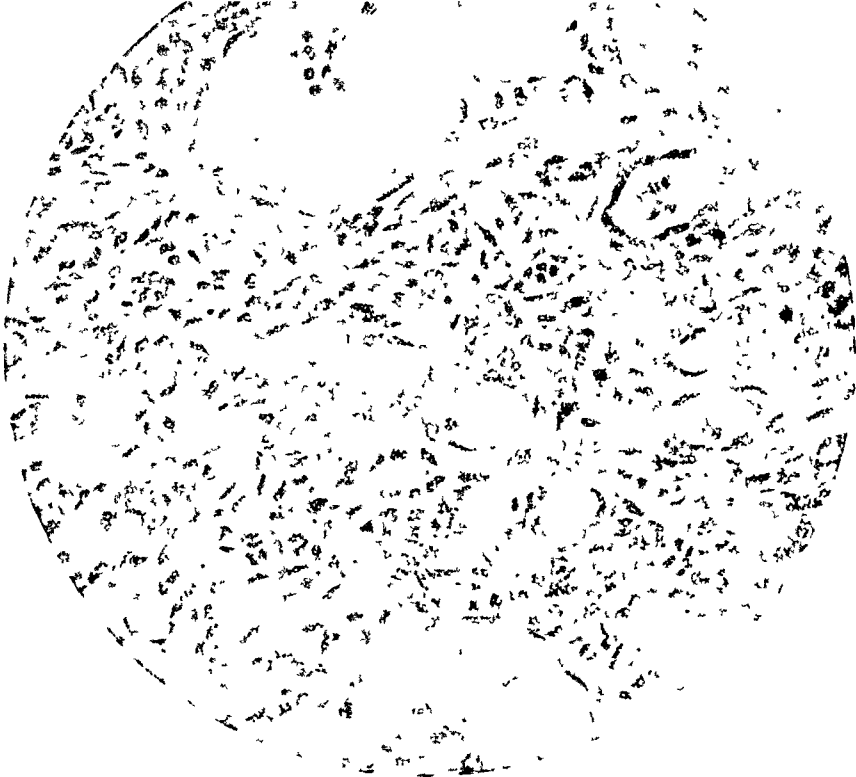


Fig. 3.—High power view of the capillary and cavernous hemangioma. The large, pale nuclei in the stroma belong to the "pseudoxanthoma" cells with their fat-laden, vacuolar cytoplasm;  $\times 250$ .

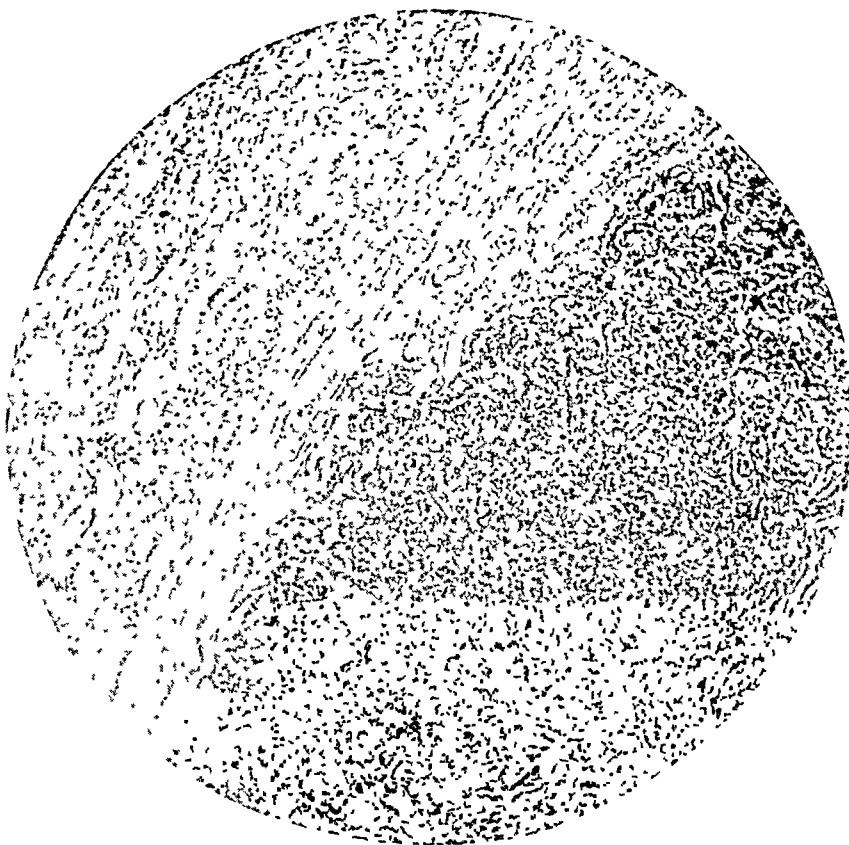


Fig. 4.—Low power view of the renal adenoma (on the right) sharply defined from the normal kidney tissue (on the left);  $\times 70$ .

## COMMENT

The writings of Lindau<sup>5</sup> and of Cushing and Bailey<sup>6</sup> leave little which my work can add to the knowledge of cerebellar hemangioblastomas. Their origin is ascribed to the vascular mesenchyme in the roof of the fourth ventricle. These neoplasms are practically confined to the cerebellum, medulla and cord, in distinction from angioma-like, congenital vascular malformations which are similarly confined to the cerebrum. Cellular, capillary or cavernous structure may predominate. They tend to become cystic, but may be solid, and all gradations exist between.

The cyst formation is held usually to be not the result of degenerative changes in the tumor, but the result of an active transudation arising from circulatory disturbances in its young vessels. This transudation may attain high pressure, and then causes necrosis of the adjacent brain tissue. Within the mural tumor, the scavenging, "pseudoxanthoma," fat-laden cells of the stroma absorb the necrotic brain substance.

No angiomatous cyst, large as the necrosis caused by its pressure may have made it, has ever been described as opening into the fourth ventricle. Simple cysts without angioma have been so described, and are regarded as developmental defects in the cerebellum. Our case is unique, therefore, in that it is the first hemangiomatous cyst reported which had a communication with the fourth ventricle. Two mechanisms may here have been in operation. The pressure by the angiomatous transudation may by necrosis of tissue have produced a larger and larger cyst in the cerebellar substance, until it finally ruptured into the fourth ventricle. Or else the disturbance of the growth of the blood vessel associated with the tumor may have determined, by deficiency of blood supply, a localized defect in cerebellar development. Whether the factor of necrosis from pressure or that of developmental defect here predominated is uncertain.

Lindau, and all investigators of this syndrome after him, emphasized the association of cerebellar hemangiomas with benign tumors in other parts of the body, and particularly its association with angiomatosis of the retina. He compared it to tuberous cerebral sclerosis, von Recklinghausen's disease and other heredofamilial syndromes, in which some external manifestation guides the diagnosis of the internal ones. The cerebellar hemangioma may find its associated tumor in the spinal cord, the pancreas, the liver, the kidneys, the suprarenal glands, the urinary bladder, the epididymis or the bones. The associated tumor

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5. Lindau, Arvid: Zur Frage der Angiomatosis retinae und ihrer Hirnkomplikationen, *Acta ophth.* 4:193, 1927.

6. Cushing, H., and Bailey, P.: Hemangiomas of the Cerebellum and Retina (Lindau's Disease), *Arch. Ophth.* 57:447 (Sept.) 1928.

in my case was a renal adenoma. Often, however, the only external sign for antemortem diagnosis is an angiomatosis of the retina (von Hippel's disease). This well recognized condition presents to the ophthalmoscope a dilated tortuous vein and a beaded artery which lead together to an angiomatic nodule somewhere in the fundus. At times this nodule may be close to the disk, but usually it is far in the periphery, so that its detection necessitates examination under a well dilated pupil.

Not always are they correlated, but if a case of von Hippel's disease is found it should be watched for the development of intracranial complications. What is even more important is that with a diagnosis of cerebellar tumor, the finding of a retinal angiomatosis establishes this tumor as an angioma. In my case, the fundi were not examined clinically. I regret that no permission could be obtained for post-mortem examination of the eyeballs. I take this occasion to reiterate Lindau's and Bailey's emphasis on the importance of examining the fundi for angiomatosis. Only by its presence can one, before operation or autopsy, distinguish between angioma and all other cerebellar tumors.

The reward of the diagnosis lies in the especially favorable surgical prospects. Practically no other cerebellar tumor gives such gratifying surgical results as does the angioma. Simple puncture of the cyst may relieve the condition for several years, while enucleation of the angioma gives permanent cure.

#### SUMMARY

A case of hemangioblastoma of the cerebellum (Lindau's disease) with formation of a cyst, unique in its broad communication with the fourth ventricle, is reported. It was accompanied by a renal adenoma. The importance of angiomatosis of the retina as a diagnostic aid in distinguishing cerebellar angioma is emphasized.

# STUDIES ON THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS \*

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In view of the well known multiplicity of bacteria isolated from endocarditic lesions, workers in this field have always more or less distinctly felt that the essential question in the pathogenesis of endocarditis is one of bacterial localization. Under what conditions will bacteria localize on the endocardium? While early experimental investigators (Wyssokowitsch,<sup>1</sup> Ribbert<sup>2</sup>) succeeded in producing endocarditis by combining the bacterial infection with a gross trauma to the heart valves, observations on experimental endocarditis without such trauma (Lissauer,<sup>3</sup> Saltykow<sup>4</sup>) have been rare until recently. Wadsworth<sup>5</sup> pointed out the relatively frequent development of fatal endocarditis in horses which had received repeated injections of killed and living pneumococci for the purpose of immunization. In this case, the preceding application of killed pneumococci appears to be the determining factor for bacterial localization on the endocardium.

Birkhaug<sup>6</sup> produced a subcutaneous focus of streptococci in rabbits with infected agar and induced endocarditis regularly by a single intravenous reinjection of the organism. As the regular production of endocarditis by a single injection of streptococci or other micro-organism has not been possible thus far, one has to infer that in Birkhaug's work the essential condition for the bacterial localization on the endocardium was the preceding establishment of a subcutaneous focus of streptococci.

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\* Submitted for publication, Aug. 24, 1929.

\* From the Western Pennsylvania Hospital Institute of Pathology, Dr. Ralph R. Mellon, Director.

1. Wyssokowitsch: Virchows Arch. f. path. Anat. **103**:307, 1886, reviewed in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie, 1924, vol. 2, p. 205.

2. Ribbert: Fortschr. d. Med. **4**:1, 1886.

3. Lissauer: Centralbl. f. allg. Path. u. path. Anat., 1912, vol. 23, no. 6; reviewed in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie, 1924, vol. 2, p. 205.

4. Saltykow: Virchows Arch. f. path. Anat. **209**:126, 1912; reviewed in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie, 1924, vol. 2, p. 205.

5. Wadsworth: J. M. Research **39**:279, 1918-1919.

6. Birkhaug: J. Infect. Dis. **40**:549, 1927.



That no relationship between this "determining factor" and the subsequent infection in the sense of specificity needs to exist was apparent in Freifeld's work.<sup>7</sup> She obtained endocarditis in rabbits with considerable regularity by repeated injections of killed streptococci and subsequent infection with staphylococci.

Kuczynski,<sup>8</sup> working on mice, injected from 0.3 to 0.5 cc. of a culture of *Streptococcus viridans* intravenously from eight to sixteen times. He frequently observed subendocardial proliferations of "typical plasma cells," comparing them with early manifestations of endocarditis in man. He did not, however, obtain processes that went beyond this proliferative stage. Silberberg,<sup>9</sup> in his work on the behavior of the "vitally stored" body against septic general infection, gave rabbits six successive daily injections of Aschoff-Kiyono's lithium carmine solution. On subsequent intravenous infection with *Staphylococcus* all the five animals employed developed endocarditis. In this case, the determining factor for bacterial localization on the endocardium was evidently the preceding application of lithium carmine. Siegmund<sup>10</sup> produced experimental endocarditis in rabbits by daily intravenous injections of rapidly increasing doses of *Bacillus coli* or *Staphylococcus*. Siegmund and Dietrich<sup>11</sup> concluded that a peculiar state of immunity, associated with an altered capacity of the endocardium to react, is the essential condition for bacterial localization on the endocardium.

Alteration of the reactivity of a host against a subsequent infection is the object of a study which we started some time ago with observations on the influence of immunobiologic processes on the course of subsequent general infections.

#### EXPERIMENTS

Guinea-pigs were sensitized by one intraperitoneal dose of 0.5 or 2 cc. of horse serum. After skin hypersensitivity was apparent (eighth to eighteenth day), the animals were infected intraperitoneally with varying doses of paratyphoid bacilli or staphylococci. With considerable regularity, an endocardial lesion developed in the sensitized guinea-pigs; this was only occasionally met with in nonsensitized controls. The lesion consisted of nodular or plateau-like mononuclear cell proliferations with occasional karyorrhexis, a process which in human pathology has been termed proliferative endocarditis.

As a sequel of sensitization to horse serum, the capacity of the endocardium to react against an infection has evidently been altered.

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7. Freifeld: Klin. Wchnschr. **7**:1645, 1928.

8. Kuczynski: Verhandl. d. deutsch. path. Gesellsch. **18**:47, 1921.

9. Silberberg: Virchows Arch. f. path. Anat. **267**:483, 1928.

10. Siegmund: Verhandl. d. deutsch. path. Gesellsch. **19**:114, 1923.

11. Dietrich: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **27**:188, 1925.

Has this altered capacity of the endocardium to react any bearing, and in what way, on the problem of the pathogenesis of human endocarditis?

In human endocarditis, the earliest endocardial change has, until recently, generally been supposed to be an "endothelial damage" preceding the localization of bacteria. This endothelial damage has never, however, actually been observed.

Mononuclear endocardial cell proliferations, on the other hand, are a well known constituent of the picture of human endocarditis. Ribbert, presenting the histology of endocarditis verrucosa (1924), referred to endocardial proliferations of large polyhedral elements as present underneath the thrombotic deposits and extending to some extent underneath the adjoining intact endocardial surface. In his presentation there is little if any doubt about the sequel of events: a hypothetical endothelial damage leads to localization of bacteria and formation of thrombotic deposits. The thrombotic masses penetrate into the valvular tissue, leading to the appearance of broad homogeneous bands. Subsequently, a secondary proliferation of large polyhedral cellular elements sets in. Although penetrating thrombotic deposits are, as he stated, hardly ever seen without the aforementioned proliferative changes, Ribbert did not seem to doubt seriously that thrombi regularly precede the cellular proliferations. Patients, he argued, do not die at a stage when the thrombi have not yet been followed by proliferative changes, and therefore one has no chance to observe these earliest stages. In this, thus far dominant, interpretation, primary endothelial damage, as well as the penetration of thrombotic masses into the tissue, remains a logical requirement of the theory, though not wholly founded on actual observations.

Autopsies on several patients who showed early endocarditis have furnished us the possibility of studying early endocardial reactions in endocarditis. In these patients, nodular monocytic proliferations were not infrequently observed underneath an intact endothelium and far from the site of thrombotic deposits (fig. 1). This observation allows the conclusion that monocytic endocardial proliferations in human endocarditis are not invariably the sequel of thrombotic deposits.

Furthermore, in several mononuclear endocardial cell proliferations, areas of transformation of the intercellular substance into hyalin were found associated with a defect of the surface endothelium, but without a thrombotic deposit. We infer, then, that in human endocarditis not only may mononuclear cell endocardial proliferations arise in the absence of thrombotic deposits, but, on the other hand, they may, through regressive changes, develop endocardial defects which in turn may become the site of thrombi.

In other words, nodular mononuclear cell proliferations of the human endocardium may precede the formation of morphologically

detectable endocardial defects and endocardial thrombotic deposits; i. e., they are one of the earliest endocardial reactions in human endocarditis.

Do identical considerations prevail in the experimental animal endocarditis? In order to approach the latter question, an endocarditis was induced in rabbits by intravenous streptococcic vaccination and subsequent infection with staphylococci (after Freifeld). It was found that the endocarditic nodule of such a rabbit consisted of large mononuclear cellular elements. Near the free surface, degenerative changes and superficial accumulation of cocci were noted. The picture has to be interpreted as a mononuclear cell proliferation followed—not preceded—by the formation of thrombotic deposits.



Fig. 1.—Human rheumatic endocarditis: nodular endocardial proliferation. One may note marked polymorphism of proliferating elements; lack of polarity; absence of definite endothelial defect and absence of thrombosis. (Zeiss, Abbe drawing apparatus; actual magnification 400  $\times$ .)

It is seen, then, that in human endocarditis, as well as in experimental rabbit endocarditis, nodular mononuclear cell proliferations represent the earliest endocardial reactions and are analogous to the endocardial reaction of the guinea-pig that has been sensitized to horse serum and subsequently infected. Are we therefore to infer that processes somehow related to that of sensitization to horse serum are one essential condition for bacterial localization on the endocardium?

In an effort to answer this question, various measures were tried to induce a true endocarditis in guinea-pigs and rabbits.

1. Intraperitoneal paratyphoid, as well a staphylococcus, infection of guinea-pigs sensitized to horse serum led to the nodular reaction of the

endocardium, but never to a true endocarditis. Desensitization after the infection did not alter the result. Desensitization before the infection practically prevented the nodular endocardial reaction. These experiences confirmed our assumption of a relationship between endocardial reaction and hypersensitiveness, but failed to furnish information as to the rôle of that reaction in the genesis of true endocarditis.

*Production of Endocarditis in Rabbits by Infection with Staphylococcus Following a Course of Intravenous Casein Injections*

Day of Experiment	Rabbits							
	J <sub>3</sub>	J <sub>4</sub>	J <sub>6</sub>	J <sub>7</sub>	J <sub>8</sub>	X <sub>1</sub>	X <sub>3</sub>	X <sub>4</sub>
1	Received	Received	Received	Received	Received	Received	Received	Received
2	5 daily	5 daily	10 daily	10 daily	10 daily	10 daily	10 daily	10 daily
3	casein	casein	casein	casein	casein	casein	casein	casein
4	injec-	injec-	injec-	injec-	injec-	injec-	injec-	injec-
5	tions	tions	tions	tions	tions	tions	tions	tions
6	Received 1.5 cc. staphylococci intravenously	Received 2 cc. of staphylococci intravenously						
8	Died							
9	.....	Died						
10								
11	.....	.....	Received 1.5 cc. staphylococci intravenously	Received 1.75 cc. staphylococci intravenously	Received 2 cc. staphylococci intravenously	Received 2 cc. staphylococci intravenously	Received 2 cc. staphylococci intravenously	Received 1 cc. staphylococci intravenously
14	.....	.....	.....	.....	Died	2 cc. staphylococci intravenously	2 cc. staphylococci intravenously	2 cc. staphylococci intravenously
16	.....	.....	.....	.....	.....	Died		
22	.....	.....	.....	.....	.....	.....	Died	
23	.....	.....	Killed	Killed				
28	.....	.....	.....	.....	.....	.....	.....	Killed
Post-mortem blood culture	Staphylococci aureus	Staphylococci aureus	Negative	Staphylococci aureus	Staphylococci aureus	Staphylococci aureus	Negative	Negative
Endocarditis	Negative	Positive	Negative	Positive	Positive	Positive	Positive	Positive

2. Guinea-pigs received five successive intraperitoneal doses of 2 cc. of polyvalent streptococcic vaccine. On subsequent intraperitoneal paratyphoid infection, one of five animals presented a marked endocardial lesion. The latter was characterized by nodular monocytic proliferations with superficial defects, beginning thrombus formation and degeneration of adjoining muscular elements—a picture which was interpreted as an early endocarditis. The remaining four showed only the nodular endocardial reaction.

3. In a third series, a nonbacterial foreign protein was substituted for the bacterial vaccine. Rabbits received either five or ten successive daily intravenous doses of 2 cc. of 2 per cent casein in 0.1 per cent sodium carbonate. After from five to ten injections, ten of fifteen animals showed at the site of the injection of the casein, a definite, and five, a less definite, allergic skin reaction characterized by a predominance of eosinophils in the resulting abscess. Subsequent intravenous infection with varying doses of staphylococci on the sixth or the eleventh day led to a definite endocarditis in six of eight cases. The course of the experiment was, in brief, as set forth in the accompanying table.

In the table, the term "endocarditis" is meant to designate histologic evidences of a primary endocardial localization of bacteria, exclusive of extensions of myocardial foci into the endocardium.

*Morphology of the Heart Lesions Induced.*—*Rabbit J<sub>3</sub>.*—The animal presented: numerous myocardial abscesses; suppurative pericarditis; nodular proliferation of endothelium in some myocardial veins; exudative periphlebitis of myocardium, and no definite endocardial lesion.

*Rabbit J<sub>1</sub>.*—Rabbit J<sub>1</sub> showed myocardial abscesses and here and there perivascular proliferation of histiocytes. In many instances, the capillary and venous endothelium of the myocardium was covered with masses of gram-positive cocci, which frequently were present also within the cytoplasm of the endothelium. Small endocardial thrombi, largely fibrinous, were found over superficial defects of the endothelial lining, without there being a marked cellular reaction of the underlying structures. Focal plateau-like thickenings of the endocardium through cellular proliferation were seen, with the appearance of intracellular eosinophilic granules outside, as well as within, the continuity of the surface endothelium. Masses of gram-positive cocci were found within the cells of these plateau-like endocardial proliferations. Here and there, a hemorrhagic infiltration of the endocardium was noted.

*Rabbit J<sub>6</sub>.*—Slight interstitial proliferative myocarditis was observed, but no endocardial lesion.

*Rabbit J<sub>7</sub>.*—This rabbit presented no marked myocardial lesion, but focal-nodular or plateau-like-active endocardial proliferations (mitoses). These foci, valvular, as well as parietal, showed intracellular cocci in a few instances. There was no endocardial thrombosis.

*Rabbit J<sub>8</sub>.*—The animal had myocardial abscesses. The changes included: (1) focal thickening of valves through cellular proliferation with the appearance of numerous polymorphonuclear leukocytes, "palisade" orientation of nuclei vertical to the surface, and bacteria within the valvular tissue, but no thrombosis; (2) at other places, similar foci showing extensive surface defects, filled with thrombotic material and masses of bacteria. The latter, in a few instances, were surrounded by large areas of necrosis, giving rise to the picture of an acute ulcerative valvular endocarditis.

*Rabbit X<sub>1</sub>.*—There were myocardial abscesses which, in many instances, were surrounded by zones of muscular calcification. Areas of necrosis were seen with calcification of muscle fibers. The valvular lesions were identical with those in

Rabbit J<sub>s</sub> (1) (fig. 2). There was no thrombosis. Small subendocardial hemorrhages were seen.

Rabbit X<sub>3</sub>.—No myocardial lesion was seen. Fibrinous endocardial thrombi were found over superficial defects of the endothelial lining.

Rabbit X<sub>4</sub>.—This animal had a slight focal interstitial proliferative myocarditis. At one place, a parietal endocardial "vegetation" was found identical in its histologic structure with the early vegetations in cases of human rheumatic endocarditis. The other changes were a nodular proliferation of large mononuclear tissue elements, cordlike hyalinization of the stroma (Ribbert's "penetrating thrombus") and early surface defect. There was no thrombosis.

*Further Observations.*—In another group of three rabbits, the intravenous treatment with casein was continued up to twenty days, a total of 60 cc. of the



Fig. 2 (rabbit X<sub>4</sub>).—Proliferative and suppurative bacterial endocarditis; no definite endothelial defect. (Zeiss, Abbe drawing apparatus; magnification 400 X).

The rabbit received ten daily casein injections, after which it was intravenously infected with staphylococci. It died two days after the infection.

solution being injected. On the twenty-first day, they received intravenous injections of 2.5 or 3 cc. of a culture of *Staphylococcus aureus*. One animal that died the following day presented fibrinous endocardial thrombi with extensive hemorrhage into the valves. The other two rabbits, which died eight and eighteen days, respectively, after the infection, did not show endocardial lesions and showed negative blood cultures. In four more rabbits the treatment with casein was extended to thirty days, a total of 90 cc. being injected. On the thirty-first day, these animals received intravenous injections of 3, 5, 5 and 10 cc. of a culture of *Staphylococcus aureus*. Three that died the following day presented a suppurative, nonthrombotic endocarditis. One animal that died ten days later yielded a negative blood culture and failed to show endocardial lesions. To summarize:

The extension of the casein treatment over twenty or thirty days did not markedly alter the results obtained in ten days.

Similar results were obtained when the intravenous infection of the animals was delayed until one, two or three weeks after the end of the treatment with casein. Two animals were employed for each stage (fig. 3).

A comparison of the morphologic observations in experimental rabbit endocarditis (figs. 2 and 3) with those in early human endocarditis (fig. 1) leads to the following inference: In the formal genesis of endocarditic lesions, mononuclear cell proliferations may constitute precursors of morphologically detectable endothelial defects.

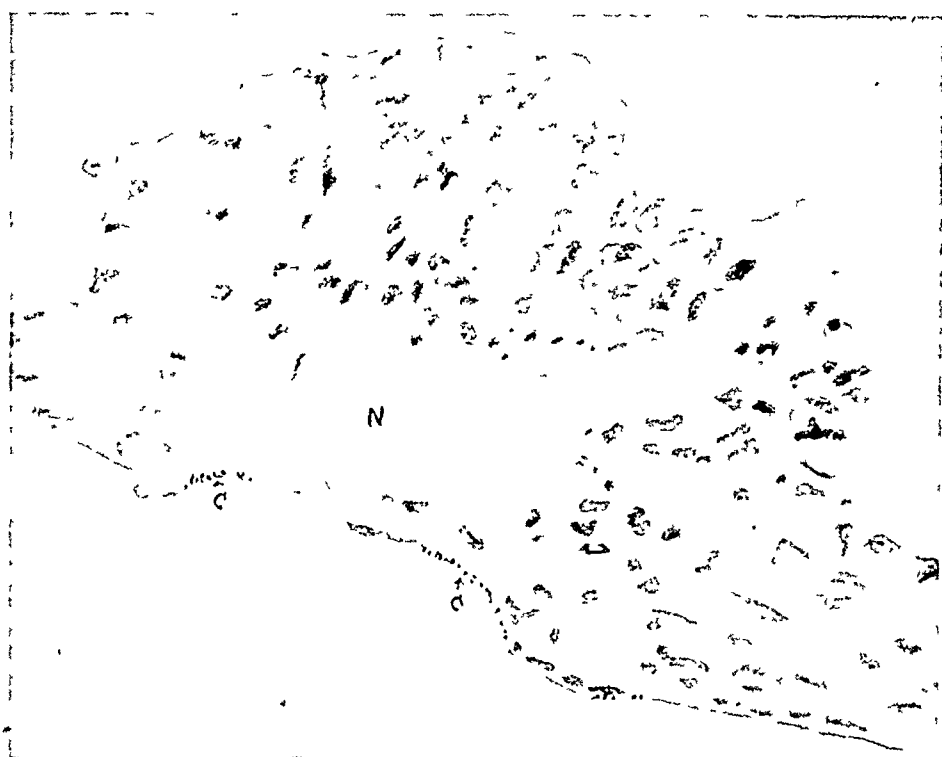


Fig. 3 (rabbit  $V_0$ ).—Large cell endocardial proliferation; necrosis (N); superficial accumulation of cocci (C). (Zeiss, Abbe drawing apparatus; magnification 400  $\times$ .)

The rabbit received ten daily casein injections, and seven days after the treatment with casein it was intravenously infected with staphylococci. It died one day after the infection.

Marked breaking down of the histiocytes of the heart valves of rabbits after the latter had received repeated injections of yatren-casein was recently reported by Pfuhl.<sup>12</sup> In four rabbits which had received twenty or thirty daily injections of doses of 2 cc. of 2 per cent casein, we have thus far not been able to corroborate this observation.

12. Pfuhl: *Klin. Wchnschr.* 8:1099, 1929.

## SUMMARY

It has been possible to modify the course of a staphylococcic bacteremia in rabbits to one characterized by endocarditic lesions. This has been accomplished in two ways: (1) by preceding the infection with staphylococci by intravenous injection of killed streptococci; (2) by preceding it by intravenous injections of casein. Although the treatment with casein, per se, has never led to morphologically detectable cellular damage, it has been a prerequisite for the development of bacterial endocarditis.

The inference that bacterial localization on the endocardium results from its altered capacity to react toward bacteria would seem logical. This relationship, however, is scarcely true within the confines of specificity, as the "allergic state," so-called, may be induced by a non-bacterial, foreign protein. It remains a matter of further study to what extent, and how, the "allergic state" referred to may be correlated with definable alterations of cellular activity.



# THE MITOCHONDRIA IN ACUTE EXPERIMENTAL NEPHROSIS DUE TO MERCURIC CHLORIDE \*

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Although mitochondria have been known for several decades, little observation has been made of the changes that they undergo in pathologic processes. The literature was recently summarized and critically reviewed by Cowdry.<sup>1</sup>

Believing that a study of the mitochondria of the cells of a single organ in response to various irritating agents would be of value in understanding the mode of action of these agents, we have undertaken to study the response of mitochondria of the kidney to various nephrotoxic agents. This report is the first of these studies. It is concerned with the changes in the renal mitochondria in response to mercuric chloride.

## METHOD

White rats derived from the Wistar stock were used exclusively. The mercuric chloride was dissolved in distilled water and injected subcutaneously into the skin of the back.

Two types of experiments were carried out: The first comprehended the administration of a dosage of 40 mg. per kilogram, and postmortem examination of two animals, each day for five days. This dosage was found to kill in about six days. The second comprehended the administration of variable dosages and postmortem examination of all the animals after twenty-four hours. The dosages employed here were 10, 20 and 40 mg. per kilogram. All animals were kept on the regular stock diet of prepared dog biscuit, cracked corn and water ad libitum. In addition, fresh raw liver and cabbage were given once a week.

When an animal was to be killed, it was stunned by a blow on the head. From 2 to 4 cc. of blood was secured by cardiac puncture, and the abdomen was opened and both kidneys were removed. In all cases, the heart was still beating when the kidneys were removed. One kidney was cut in three sagittal sections and placed in Regaud's fixative (20 per cent neutral formaldehyde in 3 per cent bichromate of potassium). The other kidney was cut into thin slices by a sharp razor; the slices were teased apart and studied after being stained with Janus green. Each experiment was run in duplicate. When the two rats used in an experiment were killed,

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\* Submitted for publication, July 12, 1929.

\* From the Department of Pathology, Ohio State University.

\* Read at the Twenty-Eighth Annual Meeting of the American Association of Pathology and Bacteriology, Washington, D. C., May 1, 2 and 3, 1928.

1. Cowdry, E. V.: The Reactions of Mitochondria to Cellular Injury, Arch. Path. 1:237 (Feb.) 1926.

a normal rat (in the same cage and under similar living conditions) was also killed and examined as a control, the tissues of this rat being subjected to the same reagents and processes. This general plan of using two rats for the experiment and one normal rat for the control was preserved throughout.

The urea nitrogen was determined according to the aeration method of Folin, 1 cc. of whole blood (anticoagulant potassium oxalate) being employed.

The blocks of kidney intended for mitochondrial stains were fixed in 20 per cent neutral formaldehyde in 3 per cent potassium bichromate, for three days, the solution being renewed each day; and in 3 per cent bichromate alone for nine days, the solution being changed every three days; washed; dehydrated in alcohol; cleared in chloroform, and embedded in paraffin. Partial serial sections were cut, one to be stained with hematoxylin and eosin, one with Bensley-Cowdry's acid fuchsin-methyl green and one with iron hematoxylin.

The technic has been given in some detail, since the interpretation of mitochondrial changes is extremely difficult even when there is abundant control

*General Relations, Structure and Function of Mitochondria as Determined in Experimental Nephrosis Due to Mercuric Chloride*

Dosage, Mg.	Lapse of Time Until Animal Was Killed, (Average), Hours	Urea N Mg.	Histologic Changes	Mitochondria of Proximal Convoluted Tubule
10	24	25	None	No change
20	24	37	Cloudy swelling pars recta; proximal convoluted tubules	Perinuclear arrangement; no qualitative change except slight increase in size
40	24	50	Same as above with beginning involvement of remainder of proximal convoluted tubule	Beginning agglutination of perinuclear mitochondria in pars recta; slight fragmentation and agglutination in first and second parts
40	48	120	Same, but slightly more severe	Same, with loss of specific supravital staining
40	72	160	Complete necrosis pars recta; marked cloudy swelling first and second parts; many hyaline casts; fat in pars recta in some cells of few cases	Complete agglutination of mitochondria in third part; moderate agglutination and marked fragmentation in first and second parts; no change in remainder of tubular system

material. All interpretations in the next section of this paper are based on a collective study of: Janus green supravital stains, acid fuchsin-methyl green, iron hematoxylin and hematoxylin and eosin stains of fixed preparations.

#### OBSERVATIONS

In the animal receiving the smallest dose of mercuric chloride, 1 mg. per hundred grams of body weight for twenty-four hours, there was no detectable change either in ordinary histologic structure or in the mitochondria, but determinations of the blood urea revealed from 23 to 30 mg. per hundred cubic centimeters.

When this dose was increased to 2 mg. per hundred grams of body weight, definite changes resulted both in the mitochondria and in the histologic appearance of the cell. This change was restricted to the third part of the proximal convoluted tubule. Histologically, it consisted of a marked cloudy swelling and granular degeneration of the

epithelial cells. The nuclei of the cells exhibited pyknosis and karyolysis. In some, the whole tubule from basement membrane out was a mass of acidophilic granular débris. This detritus, however, was not homogeneous; on close examination it was seen to be composed of masses of dense, deeply acidophilic material with a loose, coarsely granular débris between. The dense masses were rather sharply defined, and in the center of some was a pale-staining nucleus. After viewing such severely damaged cells, one expected to find the mitochondria completely destroyed. As nearly as could be determined they were in normal amount. They still retained the specific staining reaction with Janus green, but they tended toward a different arrangement. In



Fig. 1.—An early stage in nephrosis due to mercuric chloride to show the perinuclear arrangement and beginning agglutination of the mitochondria in the third part of the proximal convoluted tubule Bensley-Cowdry stain

the normal control, the mitochondria of this portion of the tubule were practically all granular with no definite arrangement, except that they rarely occupied the luminal half of the cell. As a rule, they did not extend beyond the nucleus and if so, only to a slight extent. In the kidney of the animal given mercuric chloride, at this stage the mitochondria were diffuse throughout the cell with a definite perinuclear arrangement in many cases. The masses of protoplasm lying in the lumen look not unlike eosinophilic myelocytes when stained by the acid fuchsin-methyl green method. Although in the majority of cases the mitochondria retained their identity as individual particulate matter, in a few

cases there was a tendency toward agglutination. They appeared to become more highly refractive to light and ran together, finally giving a large, strongly acidophilic, highly refractile mass. In this stage of the disease, these large masses, representing one cell, were not seen to fuse with similar masses, as will be shown later. This change, although definite, was not common at this stage. This early response to mercuric chloride has been discussed at some length, since it is evident that in the injury to the kidney from mercuric chloride, general histologic change and destruction of the mitochondria did not run hand in hand.

With dosages of 4 mg. per hundred grams of body weight, the same tubules showed a marked cloudy swelling and parenchymatous degenera-



Fig. 2—A later stage than that shown in figure 1. One may note the large masses of acidophilic material in the lumen. Ordinary stains of such a tubule reveal practically complete necrosis. Bensley-Cowdry stain.

tion of a severe grade. The nuclei were more profoundly affected. In addition to this there was a beginning involvement of the first and second parts of the proximal convoluted tubules. The epithelium was swollen and granular and the nuclei pale staining. The remainder of the tubular system was apparently normal. The mitochondria of the third part of the proximal convoluted tubule were similar to those in the previously described rat, except that agglutination was more marked. Not only were all the mitochondria of one cell fused into a large mass, but four or five mitochondria were seen fusing into a large droplet. On intravital staining, these masses appeared as highly refractile droplets, while the individual mitochondria still stained specifically. The few nuclei remain-

ing in the cells no longer took the methyl green and presented many irregular islands of chromatin, but in each nucleus could be seen one or two large, strongly acidophilic masses resembling nucleoli. Apparently, the basic chromatin had been agglutinated and changed to oxychromatin. In the first and second parts of the proximal convoluted tubule, the chromatin of the nucleus was agglutinated and changed to oxychromatin. The rod-shaped mitochondria were agglutinated into deeply acidophilic masses. Granulation of the rods was not a prominent feature, but in most cases the mitochondria appeared to retain a normal morphology up to the moment of fusion with adjacent rods. The single mitochondria retained their specific supravital staining power, but after fusion lost it.

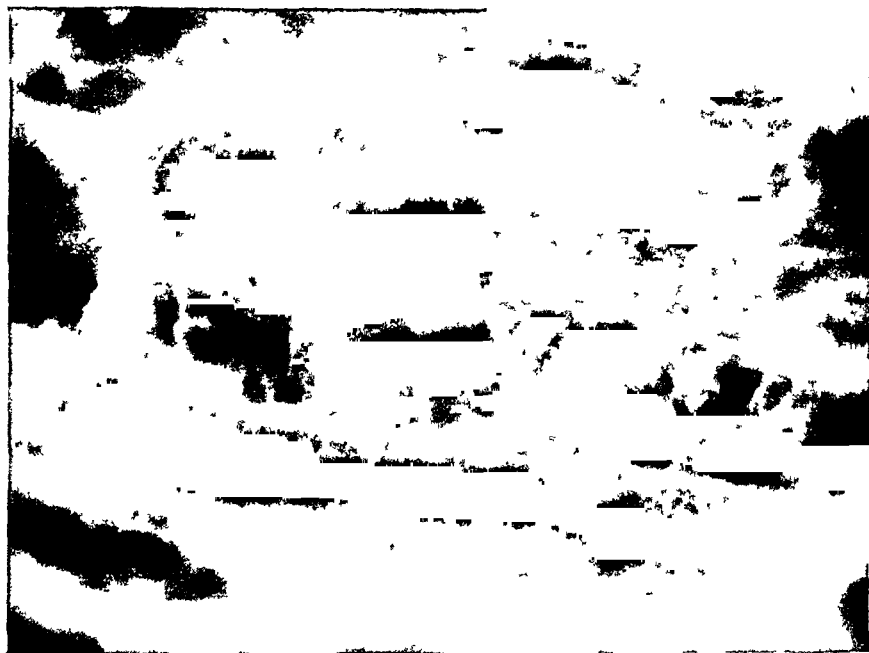


Fig 3—A late stage in nephrosis due to mercuric chloride<sup>4</sup> Three descending limb tubules are filled with necrotic material with complete agglutination of the mitochondria. One may note the one ascending limb with intact mitochondria and its lumen filled with a hyaline cast. Bensley-Cowdry stain

At this stage, the extremely small rod-shaped mitochondria in the endothelial cells of the glomeruli and in the cells of Bowman's capsule did not differ in morphology from the normal. At this stage, many hyaline casts were to be observed, especially in the distal convoluted tubules. The mitochondria in these tubules even when they contained a cast were regular in shape, size and distribution.

When histologically the tubular epithelium was a homogeneous granular detritus, mitochondria stains gave a deeply acidophilic mass, in some cases somewhat irregular, in others homogeneous. Individual mitochondria could no longer be resolved. The process of agglutination was complete. Even when the process had gone on to complete necrosis

in the third part of the proximal convoluted tubule, the mitochondria and the general appearance of the first part remained fairly well defined. It is only in the most severe nephropathy from mercuric chloride that these cells showed definite agglutination and granulation.

In summary of the mitochondrial changes in the progression of tubular nephrosis due to mercuric chloride in the white rat, it may be said: that the injury even from fairly large doses is definitely restricted to the proximal convoluted tubule, first involving the third portion of the convoluted tubule, later invading the remaining parts; that there are marked histologic changes in the cytoplasm and nucleus with definite retention of nitrogen before the mitochondria show any pathologic



Fig. 4.—A tubule from the upper portion of the proximal convoluted tubule. One may note the prominent acidophilic chromatin mass in one nucleus and the general preservation of rod mitochondria. This kidney showed severe change in the lower portions of the proximal convoluted tubules. Bensley-Cowdry stain.

alteration other than that of position; that morphologically the mitochondrial alteration is essentially an agglutinative process and not a fragmentation of rods into granules; that the chemical nature of the mitochondrial change is not predominantly a fatty metamorphosis, but rather the formation of an acidophilic mass probably albuminous, and finally that there is retention of nitrogen in the blood before there are morphologic changes in the kidney. Function and morphology considered together, the order of events is about as follows: nitrogen retention, parenchymatous degeneration of the cytoplasm, agglutination and to a less extent fragmentation of the mitochondria and, last, complete death of the cell.

## COMMENT

From these observations it is evident at once that mitochondria are not always the most sensitive indicator of cell injury. Evidently, the response of mitochondria depends not only on the cell involved, but also on the irritant applied. Strongman<sup>2</sup> and McCann<sup>3</sup> showed that in poliomyelitis, even when the Nissl substance of the nerve cells has undergone partial chromatolysis, the mitochondria retain their usual morphology. Likewise, Marinesco and Tupa<sup>4</sup> demonstrated that the mitochondria of nerve cells are little affected by division of their axones. Against these observations that mitochondria are fairly resistant, we have the fact of their extreme susceptibility in the glandular organs to drying, pressure and other slight mechanical or chemical injury. Further, Oliver<sup>5</sup> observed that in the guinea-pig the mitochondria in the proximal convoluted tubule of the kidney change in morphology during diuresis. He reported granulation of the rods during active urinary secretion, this in some cases going to the point of resembling the definite changes described by others as pathologic. Similar changes have been reported by other investigators. The variability of mitochondrial injury is further emphasized by the observations reported here. Even when the mitochondria of the third part of the proximal tubule are completely destroyed, a distal tubule separated from it only by a few microns presents no deviation from the usual appearance. The final interpretation must be that the injury to mitochondria is dependent on their own inherent properties varying with the cell type and with the nature of the injury. Most emphatically they are not universal indicators of cell injury, as has been assumed by some.

Cowdry,<sup>6</sup> in attempting an explanation of the function of the mitochondria, proposed to utilize the physicochemical phenomenon of adsorption at the mitochondrial cytoplasmic interface. He held that there is an analogy here to the specific adsorption of Janus green. From a 1:500,000 solution, mitochondria will concentrate it so that they become visible in a layer 0.5 micron thick. In further support of this, we have the observations of Oliver,<sup>5</sup> using the methods of Leschke. He reported

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3. McCann, G. P.: A Study of Mitochondria in Experimental Poliomyelitis, *J. Exper. Med.* **27**:31, 1918.

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that urea is present in the proximal convoluted tubule in direct proportion to the amount being excreted and that on microchemical precipitation with acid mercuric nitrate, granules are found lined up in the cells in an arrangement similar to that of the mitochondria. The conclusion is that the urea is concentrated or condensed by the mitochondria and that they serve as the means of urea excretion. The position is further strengthened by the observations that the regenerated cells in nephritis due to uranium contain ill defined mitochondria and little or no urea. Interesting also are the observations of different investigators (Aschoff, Gross) that the vital dyes are stored in the proximal tubules by the mitochondria.

The limitations of the applications of morphologic study are not far removed from the simple statement of the observations, yet with the interfacial adsorption theory of Cowdry, it appears that some pathologic conditions may be explained. With ordinary physicochemical adsorption at interfaces, poisoning is a well known phenomenon. For example, platinum black electrodes saturated with hydrogen in a solution of hydrogen ions are rendered useless by a trace of arsenic in the solution. The electrode is said to be "poisoned." In the present report, the observation has been made that there is a retention of urea before the mitochondria are morphologically changed. Assuming that the mitochondria act as condensers to excrete urea, we may postulate that they also condense mercuric chloride and in so doing "poison" the interface so that urea is no longer adsorbed from the blood stream. The result would be a retention of urea in the blood stream. As a mercuric salt is further concentrated by the mitochondria, it comes to a concentration in which it acts on the remainder of the cell and causes its necrosis. The observation that agglutination is a prominent feature in the response of the mitochondria to nephrosis due to mercuric chloride certainly indicates that there is some disturbance in the interfacial tension between the cytoplasm and mitochondria. According to such a theory of the action of mercury in producing renal injury, the initial alteration is an adsorption and "poisoning" of the mitochondrial cytoplasmic interface with a change in the surface tension at this interface. Later, the mercury with increasing concentration acts as a general cytoplasmic poison and kills the entire cell.

#### SUMMARY

Retention of nitrogen in the blood occurs in nephrosis due to mercuric chloride in the white rat before there are demonstrable changes in the morphology of the kidney. There are definite changes in the cytoplasm and nucleus of the proximal convoluted tubule before the mitochondria show any qualitative change. It is suggested that mercuric chloride produces nephrosis by adsorption on the surface of the mitochondria, "poisoning" the interface and later killing the cell.



# PRIMARY CARCINOMA OF LIVER WITH METASTASIS TO BONE\*

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The purpose of this report is to record a primary carcinoma of the liver presenting an extremely rare feature, that of skeletal metastasis. Primary carcinoma of the liver is itself an uncommon lesion, and it rarely forms metastases except in the lungs; in this instance, it gave rise to a large secondary growth in the neck of the femur, causing spontaneous fracture. The neoplastic proliferation was of liver cell type.

## REPORT OF CASE

A negro laborer, aged about 45, in the act of lifting, felt his right leg suddenly give way, and he fell to the ground. Previous to this, he had not complained and had worked continuously. Roentgen examination revealed a fracture of the neck of the right femur and evidence of local rarefaction of bony tissue about the fracture. The usual procedure of immobilization in extension and abduction was carried out consistently. There was no evidence of effective healing of the fracture. Six weeks later, the fragments were still mobile, and x-ray pictures showed a deficiency of callus formation. The patient lost weight and strength steadily. Ascites developed, and the fluid was removed repeatedly by cannula. There was no history suggestive of syphilis, but inequality of pupils and a strongly positive Wassermann reaction of the blood caused a suspicion that syphilitic infection of the femur and of the abdominal viscera might be responsible for his condition. Vigorous antisiphilitic treatment was not effective. There developed a progressive anemia of secondary type. The urine contained bile and a small amount of albumin. An indefinite mass was palpable in the epigastric region slightly to the left. An exploratory laparotomy revealed a cirrhotic liver with the possibility of carcinoma or syphilis. The mass consisted of omentum matted together. The abdominal wound did not heal. The patient died nine weeks after the occurrence of the spontaneous fracture. A definite clinical diagnosis had not been made. Bilateral bronchopneumonia, hypostatic in character, was the terminal development.

*Postmortem Examination.*—The body was that of a markedly emaciated negro about 5 feet 11 inches (150 cm.) tall, apparently 45 years of age and weighing about 90 pounds (40.8 Kg.). The muscles and subcutaneous tissues were wasted. The bony landmarks stood out prominently. The pupils were unequal. Several teeth were missing; the mouth was foul. No lymph nodes other than the inguinal ones were palpable. A surgical wound about 15 cm. in length extended from the level of the tip of the xyphoid process to the level of the umbilicus, slightly to the right of the midline. The deep and the superficial sutures were in place. The wound had gaped for a distance of 4 cm. There was evidence of an imperfect healing process. The right femur was approximately  $1\frac{1}{4}$  inches (3.11 cm.) shorter than the left.

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\* Submitted for publication, June 25, 1929.

\* From the Department of Pathology, Jefferson Medical College.

The right leg was encased in extension bandages of adhesive tape. A palpable mass was present in the region of the great trochanter and neck of the right femur. The mass lay outward from the descending ramus of the ilium and was about 6 cm. in extent, firm and globular. On incision, the mass was found to comprise the neck of the femur and the distended capsule of the joint. The neck of the femur was disunited near the head. The capsule enclosing the joint contained a quantity of curdlike, greenish-yellow material, which was not pus. There was no evidence of callus formation about the ends of the fractured bone. The shaft of the femur below the trochanter was apparently normal, and the outer shell was of normal thickness and consistency. There was no change in the bone-marrow. In the neck of the femur at the point of fracture, the outer shell was not demonstrable, except for a narrow portion in the anterior surface about 8 mm. in width. The ends of this portion were sharp and jagged as if recently fractured. All the rest of the neck of the femur was soft and pulpy. The cancellated bony tissue was eroded extensively, and the remnants of it had greenish-yellow, bile-colored material in the interspaces. The upper rim of the acetabulum was eroded, and on its surface there were quantities of the described bile-colored, curdlike material.

The subcutaneous fat was absent. The skeletal muscles were pale. The omentum did not cover the bowels anteriorly. It was curled up and matted into a mass that occupied the upper portion of the epigastrium. This mass involved the left lobe of the liver and extended to the level of the umbilicus. The right lobe of the liver lay 4 cm. above the costal margin. The pyloric end of the stomach and the duodenum were slightly adherent to the mass described. When separated from it, their structures were found intact. The right lobe of the liver was shrunken, firm and nodular, presenting the typical hob-nailed appearance of atrophic cirrhosis. It cut with increased resistance. On incision, the liver revealed numerous vessels, apparently radicles of the portal vein, containing a yellowish curdlike substance which had a greenish tinge, as if from bile. The tumor mass that involved the left portion of the liver consisted of numerous nodules of a greenish-yellow color and from 0.5 cm. to 2 cm. in diameter. In places, these masses had a putty-like consistence, and varied in color from greenish to brownish. Approximately a hundred such nodules were seen in one section. Numerous such nodules were seen beneath the capsule of the liver.

The portal vein anterior to the foramen of Winslow was completely filled with a mass of soft, pulpy, curdlike, greenish-yellow material similar in all respects to that found in the hepatic branches of the portal vein and in the soft nodules in the liver substance. The mass extended for a distance of 5 cm. along the portal vein. It was found for a short distance below the entrance of the splenic branch. Beyond this point, the portal vein and its mesenteric tributaries were unobstructed.

The wall of the gallbladder was slightly thickened. It showed no involvement by the neoplastic growth. It contained about 60 cc. of black, tarry bile and no concretions.

There were a few adhesions about the upper and posterior portions of each pleural cavity. The right lung was heavy, wet and boggy in its posterior portion, and on section, quantities of blood-tinged, frothy fluid escaped. In the extreme posterior portions, there was almost complete consolidation. The anterior portion contained air throughout and crepitated normally under pressure. The condition of the left lung corresponded with that of the right. Approximately one fourth of the total lung substance was partially consolidated.

The heart was rather small, pale and flabby. The heart valves were apparently normal, and the musculature was of normal firmness.

The intima of the aorta in the ascending portion and the arch contained irregular areas of yellowish and translucent elevations intermixed with puckered and wrinkled depressions. On section, these areas did not contain either calcified or atheromatous material. The descending aorta was not involved.

The spleen was moderately enlarged; its capsule was smooth and contained no scars. On section, an excess of fibrous tissue was found in the splenic pulp. There were no other visible changes.

The entire visceral and parietal peritoneum showed deep injection and was of a purple cyanotic color. The walls of the intestines were relaxed and atonic.

The pancreas was apparently normal. Near the head of the pancreas, were several enlarged lymph nodes. These were grayish white and showed no gross evidence of neoplastic involvement.

There were no other visible abnormalities about the abdominal viscera.

The left kidney was of normal size and configuration. On section, the cortical portion was found increased in thickness and pale. The cortical markings were accentuated, and the capillaries were congested and prominent. A small amount of turbid, apparently purulent fluid could be pressed out of the papillae. The right kidney was somewhat more congested; otherwise it showed the same conditions as the left.

The bladder contained about 100 cc. of brownish, turbid urine. The mucosa appeared to be normal. The musculature of the wall showed no visible changes.

*Anatomic Diagnosis.*—Primary carcinoma of the liver, with marked destruction and replacement of liver substance; obstruction of the portal vein by the carcinomatous growth; metastatic carcinoma in the neck of the femur, with absorption and destruction of bony tissue, and ununited fracture; atrophic cirrhosis of the liver; bilateral bronchopneumonia; parenchymatous degeneration of the kidneys; toxic degeneration of the heart muscle; fibrosis of the spleen, probably syphilitic; syphilitic aortitis; passive congestion of the abdominal viscera; moderate localized peritonitis; unhealed surgical incision of the abdominal wall; marked generalized emaciation.

*Histologic Diagnosis.*—Liver: Atrophic cirrhosis; primary carcinoma of the liver cells; carcinomatous masses distending the lumina of the portal veins.

Bone (Neck of Femur): Metastasis of carcinoma from the liver; rarefaction and destruction of the bone substance; deficiency of the healing process.

Lung: Marked passive congestion; metastases of carcinoma from the liver in the peribronchial lymphatics; edema; bronchopneumonia.

Kidney: Congestion; moderate granular degeneration of the tubular epithelium.

Lymph Nodes: Moderate hyperplasia of some; atrophy; fibrosis; beginning calcification of others.

Heart Muscle: Granular degeneration; rarefaction; pigmentation.

Aorta: Degeneration and rarefaction of the intima; cellular infiltration in the adventitia and about vasa vasorum; syphilitic aortitis.

Spleen: Moderate diffuse increase in the stroma; atrophy of the follicles and of the pulp; passive congestion.

Pancreas: Moderate passive congestion; moderate parenchymatous degeneration.

The wall of the bladder, prostate, suprarenal glands and gastro-intestinal mucosa contained no significant features.

*Microscopic Examination.*—Sections of the liver consisted almost entirely of irregular dense bands of fibrous tissue (fig. 1) enclosing various-sized nodules of carcinoma. Many of these nodules were necrotic; others showed evidence of recent growth and proliferation. All such nodules contained bile pigment, both intracellular and extracellular. The carcinomatous cells were slightly smaller than normal liver cells and their cytoplasm was slightly more densely stained. They occurred in dense masses entirely without arrangement. The cells in the masses within the portal veins and in the mass found in the neck of the femur were entirely similar to those in the liver nodules. They also contained bile pigment. The bands of fibrous tissue in the liver were even more dense than those usually found in advanced portal cirrhosis. This fibrous tissue contained numerous proliferated bile ducts and masses of cells representing unsuccessful attempts at bile duct formation. These masses, groups and strands of cells were so irregular

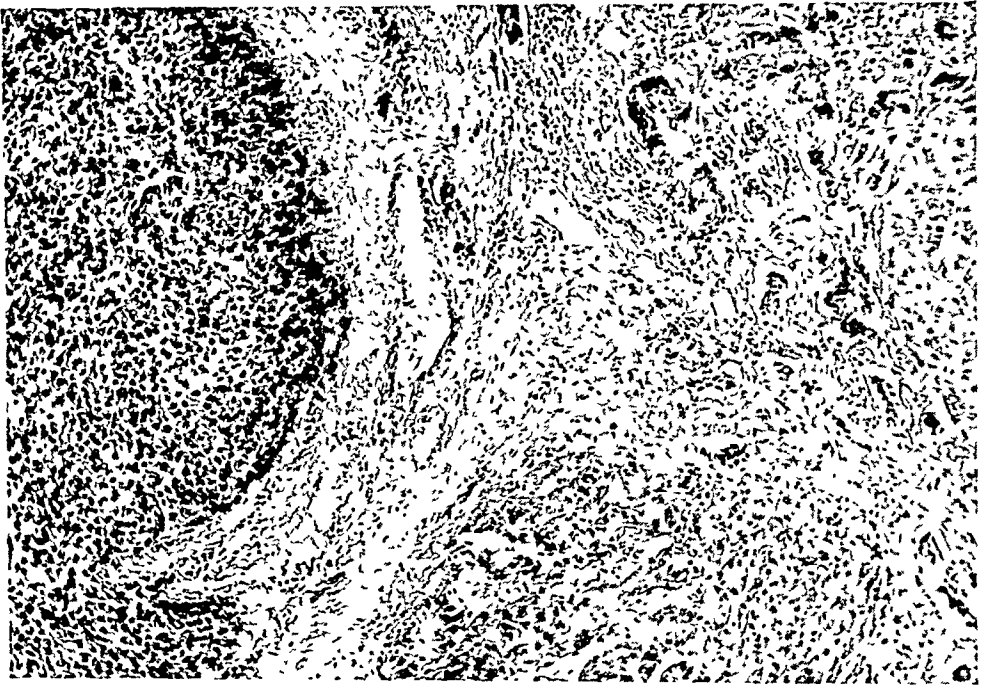


Fig. 1.—Low magnification of a portion of a carcinomatous nodule, showing fibrous tissue containing proliferated bile ducts and groups of fairly normal liver cells.

that they also resembled neoplastic proliferation (fig. 2). Careful study was required to determine this point. There were few areas containing recognizable liver tissue. In such areas, the liver cells were evidently recently formed and seemed to originate directly from bile ducts or from masses of proliferated bile duct cells. There was moderate infiltration by lymphocytes in the bands of fibrous tissue.

Sections from the neck of the femur at the site of the spontaneous fracture showed marked rarefaction and absorption of the trabeculae of the cancellated portion and of the outer shell of compact bone. The spaces in the spongy portion contained no marrow cells or fat, but were filled with masses of neoplastic cells having the same characteristics as those seen in the liver and in the thrombotic masses in the portal veins (fig. 3 B and C). These cells contained bile pigment,

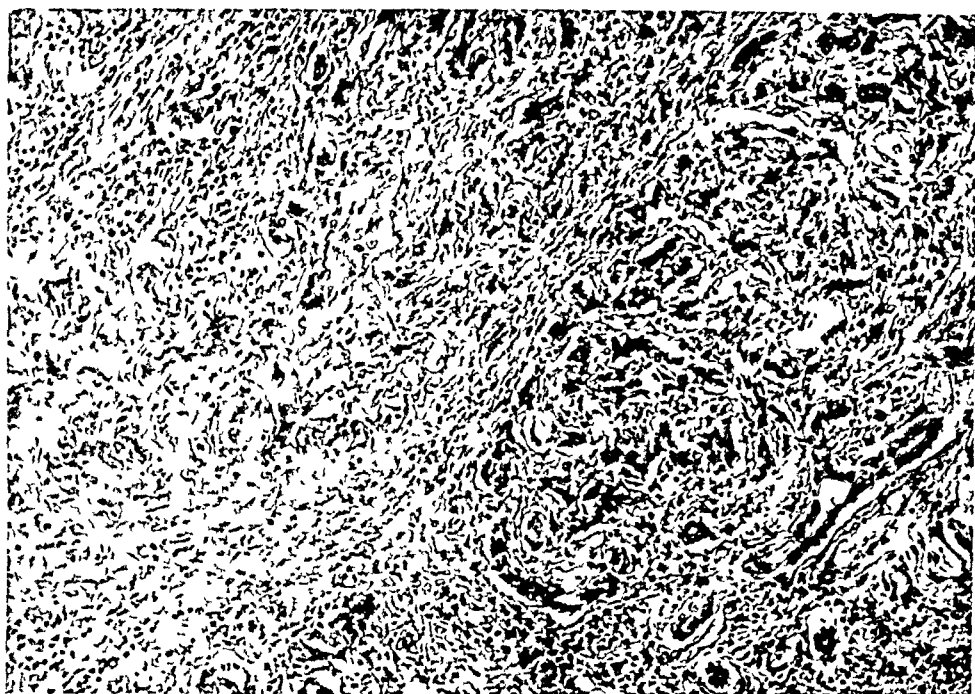


Fig. 2.—Low magnification of fibrous tissue with leukocytic infiltration. This area contains a proliferation of bile ducts so irregular that it resembles neoplastic growth of bile ducts.

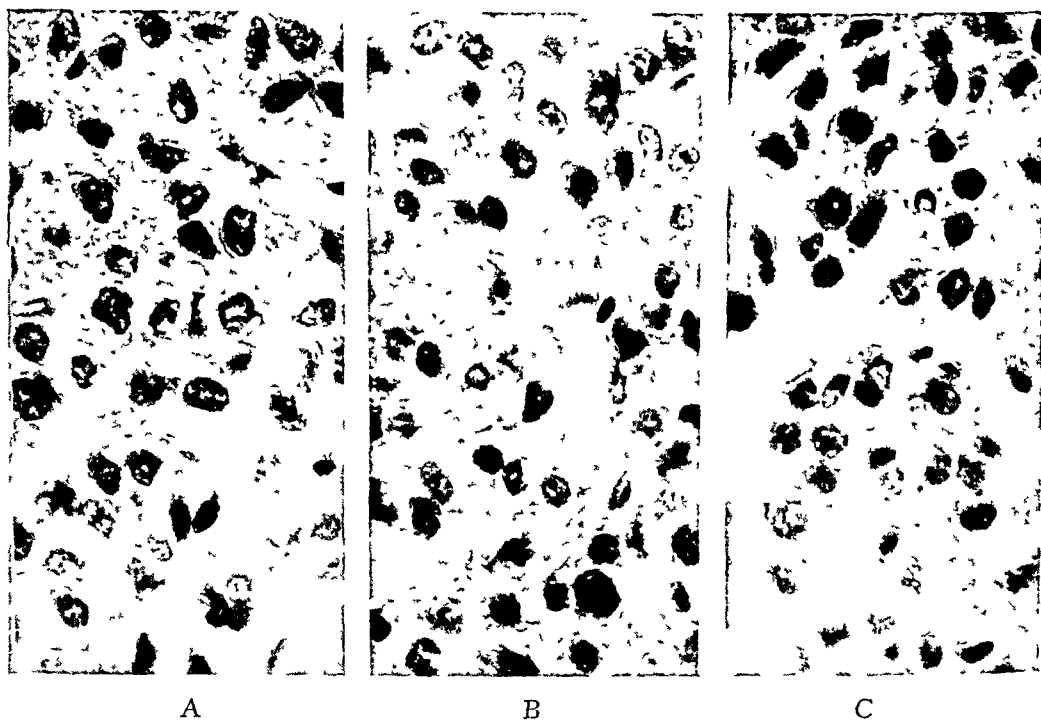


Fig. 3.—The 4 mm. objective, ocular  $\times 10$ , was used here. One may note carcinomatous cells in a liver nodule (A); growth at the site of spontaneous fracture (B); the thrombotic mass in the portal vein (C).

as did the neoplastic cells in the other locations. This observation suggests that bile pigment is formed by the cells of the liver rather than elsewhere in the body, and that the carcinomatous cells in this case retained that functional capacity. There were small areas of soft, imperfect newly formed bone, which was immature and showed no calcification.

Sections from the lung showed small masses of carcinomatous cells within the lymph spaces along the bronchial structures. No masses visible to the unaided eye were found. The cells in the lymph spaces had the characteristics of those seen in the nodules in the liver, in the thrombi within the portal veins and in the metastasis in the femur.

Cases of primary carcinoma of the liver with metastasis to bone are rare. Kauffmann<sup>1</sup> recorded two such cases. In one there were metastases in the vertebral bodies, ribs, lungs and lymph nodes; in the other, there were metastases in the abdominal lymph nodes and sternum. Catsaras<sup>2</sup> reported one case of liver cell carcinoma, with metastases in the head and neck of the right femur resulting in spontaneous fracture of the shaft below the great trochanter. Schmidt<sup>3</sup> reported a case with metastases in the frontal bone, the sternum and the pelvis. In this case, metastases were also present in the dura and the lungs. Extension of the growth had involved the portal vein. Blumberg<sup>4</sup> reported a case in which there was metastatic involvement of the twelfth dorsal vertebra and of the kidney. I have been unable to find record of other cases of skeletal metastases arising from primary carcinoma of the liver.

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# WHOOPING COUGH

## THE SITE OF THE LESION \*

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AND

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The study of the specific lesions in pertussis is usually based on human material with fatal pulmonary involvement. Arnheim's <sup>1</sup> pioneer work on the microscopic examination of expectorated mucus and stained sections of the respiratory tract appeared before Bordet and Gengou <sup>2</sup> had announced the discovery of *Bacillus pertussis*. Mallory and Hornor <sup>3</sup> found in fatal whooping cough an abundance of pertussis-like bacilli between the cilia of the trachea and bronchi. They described no characteristic lesion, and inferred that the trachea was mainly involved. Heinrichsbauer <sup>4</sup> recently substantiated Dominici's <sup>5</sup> observation that in fatal pertussis the larynx may show microscopic areas of necrosis. This lesion is not specific, as it was not constant, and was found also in fatal measles. Pospischill <sup>6</sup> has long maintained that "pertussis seems to be anchored in the lung; here is found its essential, most important and clinically classic manifestation." Feyrter's <sup>7</sup> excellent monograph on the lesions of the lung in pertussis was based on 225 postmortem examinations, in 100 of which he studied the material histologically. The investigation did not include the rest of the respiratory tract, nor any detailed study of the bacteria. He said, in summary: "The lung becomes diseased early in the course of pertussis. . . . Pertussis peribronchitis is the cause of the frequent long duration of pertussis lung disease. . . . In the bronchiolitis and peribronchio-

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\* Submitted for publication, Sept. 18, 1929.

\* From the Evanston Hospital.

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litis (not in the bronchitis) does pertussis bronchopneumonia have its origin." Smith<sup>8</sup> found *B. pertussis* not only in the trachea and bronchi, but also in the alveoli in seven of eight fatal cases of pertussis bronchopneumonia.

#### MATERIAL

Our work on experimental pertussis in young monkeys<sup>9</sup> provided exceptional material for study of the respiratory tract in benign pertussis and in early pertussis bronchopneumonia. The complete respiratory tract of one infant (Peter K.) and the larynx, trachea and bronchi of three others who died of convulsions in the catarrhal stage or early in the paroxysmal stage were also available.<sup>10</sup> This investigation deals primarily with the regional bacteria and the histologic changes of the larynx, trachea, bronchial tree and alveolar parenchyma. Ringtail monkey R2 was chosen because the course of the disease in this animal resembled that commonly encountered in young children who recover without complications. Infant Peter K. died at the onset of pertussis bronchopneumonia twelve days after the cough began. Rhesus monkey A5 had severe paroxysms for a week before he showed clinical signs of pertussis bronchopneumonia. The postmortem examinations were performed while body heat was still present. After the respiratory tract of each was examined with a hand lens for visible changes, smears and cultures were taken of larynx, trachea, bronchi and lungs. Pieces of the fixed specimens were embedded in paraffin and sectioned. Of the various stains used that of Gram, counterstained with carbolfuchsin, proved best for bacteria and cilia, whereas hematoxylin-eosin gave the best differentiation for the histologic material.

#### OBSERVATIONS

Two young male ringtail monkeys (R1 and R2) arrived on Dec. 31, 1925. The respective weights were 1,700 Gm. and 2,000 Gm.; the hemoglobin was 70 and 75 per cent; the average leukocyte counts were 7,350 and 9,100 per cubic millimeter. They resisted several nasal and throat inoculations with *B. pertussis*. On Jan. 25, 1926, they were given 2 cc. of a fresh *B. pertussis* suspension intralaryngeally. February 2 both animals sneezed and had a slight, infrequent cough. During the following days, the cough increased in severity and frequency. Within a week, they coughed in paroxysms. Lacrimation frequently accompanied the paroxysms of coughing. Many consisted of more than 20 "hacks." Never was a characteristic whoop heard. The leukocyte count in R2 exceeded 38,000, and lymphocytosis reached 89 per cent. They vomited mucus at the end of severe paroxysms, after which they usually appeared exhausted. February 13, the cough was not growing worse, and lymphocytosis had decreased. As both animals were apparently recovering, R2 was killed for study of the respiratory tract.

MONKEY R2.—The essential postmortem observations were as follows: The lining of the epiglottis, larynx and trachea was pale and pearly white, except for three minute, bright red hemorrhagic areas in the wall of the larynx. The largest measured 4 by 2 mm., the smallest, 2 by 2 mm., the other, 3 by 2 mm. There was some tenacious, transparent mucus in this vicinity. Smears contained leukocytes

8. Smith, L.: The Pathologic Anatomy of Pertussis, Arch. Path. **4**:732 (Nov.) 1927.

9. Sauer, L., and Hambrecht, L.: Experimental Whooping Cough, Am. J. Dis. Child. **37**:732 (April) 1929.

10. These specimens were kindly sent by Professor Feyrter.



and an abundance of gram-negative bacilli. No other micro-organisms were found. There were several barely visible, superficial hemorrhagic spots on the posterior tracheal wall just below the larynx; otherwise the surface of the trachea was pale, smooth and glistening. The lungs appeared normal in color and consistency; the surface was smooth, and when the material was sectioned, no areas of consolidation or other changes were seen. The tracheobronchial lymph glands were slightly enlarged.

Examination of stained sections of the larynx failed to reveal the minute hemorrhagic areas described, nor was anything resembling a lesion found. Most of the cilia were intact, and relatively few bacilli were found between and on them. Stained sections of the trachea showed in places aggregations of pertussis-like bacilli. The epithelium and submucosa appeared normal without any signs of inflammation.

Examined under low power, stained sections of the lung appeared more or less normal. The larger bronchi were relatively free from content; some had a thin layer of mucus and débris in contact with the epithelial layer. A few of the smaller bronchi contained mucus, débris and cell elements, and had definite infiltration of the epithelium and submucosa. One was found in which the lumen was almost filled. There were regions of atelectasis in the vicinity of these smaller bronchi. Here the alveolar septums appeared definitely thickened and infiltrated, and some of these alveoli were filled with cell elements. The blood vessels were not engorged, but a few of the larger ones lying near diseased bronchi had adjacent areas of infiltration (fig. 1A).

Under oil immersion, the mucus and débris in the large bronchi contained polymorphonuclear leukocytes and occasional mononuclear cells. In the submucosa there were aggregations of polymorphonuclear leukocytes. The material which partly filled some of the smaller bronchi consisted of desquamated epithelium, lymphocytes, plasma cells, mast cells and a few polymorphonuclear leukocytes. The epithelium and submucosa of these bronchi showed definite infiltration with round cells. On the ciliated epithelium of some of the bronchi, clusters of pertussis-like bacilli were seen. The areas of infiltration adjacent to some of the larger blood vessels consisted of lymphocytes, plasma cells and mast cells. These changes showed the presence of endobronchitis with a slight degree of peribronchitis. Some of the bronchioles showed similar infiltration but of less degree. On the epithelium, a few pertussis-like bacilli were seen (fig. 1B). Capillaries in the vicinity of a bronchiole which had its lumen partly filled appeared somewhat infiltrated. There was a mild endobronchiolitis and peribronchiolitis. All the alveoli, except those in the vicinity of diseased bronchi, appeared normal. Bacilli were never found in them, although diligently searched for.

PETER K.—The infant, Peter K., aged 3½ months, had never been ill until he contracted pertussis from his sister, in spite of three "prophylactic" injections of pertussis vaccine as soon as the diagnosis had been made in the older child.<sup>11</sup> The cough began twelve days before death. The paroxysms became severe twenty-four hours before admission to the hospital. He never whooped. When admitted (five hours before death) he was having convulsions, with cyanosis during paroxysms, and rapid, audible respirations. The rectal temperature was 106 F. (41 C.); the pulse, 160; the respirations, 60. Shortly before death, the child expectorated tenacious, dark red, frothy mucopus. Clinical diagnosis: Pertussis with convulsions and beginning bronchopneumonia.

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11. Sauer, L., and Hambrecht, L.: Whooping Cough, Vaccine Therapy or Early Diagnosis, *J. A. M. A.* **91**:1861 (Dec. 15) 1928.

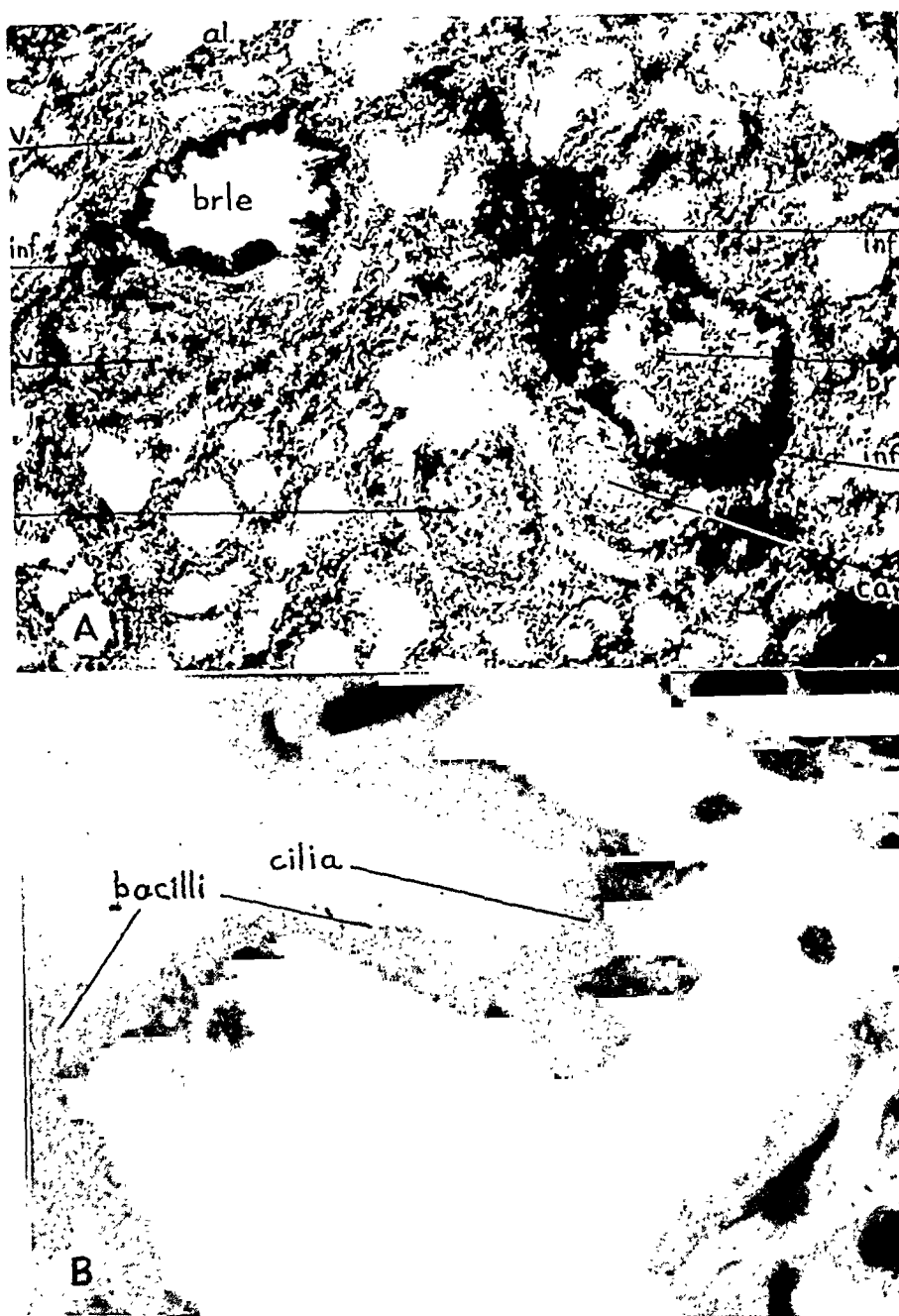


Fig. 1 (ringtail R2).—Experimental pertussis. *A*, lung showing endobronchitis and peribronchitis; × 70. *Al* indicates alveolus; *br*, bronchus; *brle*, bronchiole; *car*, cartilage; *inf*, infiltration, and *v*, vessel. *B*, bronchiole, showing ciliated epithelium with pertussis-like bacilli; × 1,500.

Dr. J. Lisle Williams' postmortem report (abridged) was as follows: "This is the body of a well developed male infant, about 3 months old, weighing about 12 pounds (5.4 Kg.). . . . The lining of the nasopharynx, epiglottis, larynx and trachea is smooth and pale. There is a little thin mucus in the trachea. . . . The tracheobronchial lymph glands are slightly enlarged, soft and pink. The lining of the left main bronchus contains only mucus in both the lower and eparterial branches. . . . The pleural sacs are normally free, and are free of fluid. In the back part of the upper and lower lobes of the right lung there are about 15 small, dark red and partially consolidated patches; in the back part of the left lower lobe there are a few, small, similar places. . . . Surfaces made by sectioning the right and left lungs disclose these dark red areas (sections). Some of these patches which are adjacent to the pleural surface resemble atelectasis.

"Microscopic: . . . Lungs: Here are seen small areas in which the alveoli are filled with fibrin, leukocytes and erythrocytes; numerous small patches of atelectasis, chiefly about the bronchi; increased fibrous tissue about the bronchi with lymphocytic and leukocytic infiltration. The bronchi are filled with leukocytes, lymphocytes, desquamated epithelium and granular debris. There is engorgement of the capillaries, especially about the bronchi and in the areas of bronchopneumonia. . . ."

Examination of stained sections of the larynx revealed nothing resembling a lesion. Most of the cilia were intact, and relatively few bacilli were found on or between them. Sections of the trachea showed aggregations of gram-negative bacilli; the epithelium and submucosa appeared normal with no sign of inflammation.

Under the hand lens, the stained sections of the diseased areas of the lung showed regional atelectasis and dense infiltration, most pronounced around bronchi and blood vessels. This density was in direct proportion to their proximity. The blood vessels in these centers appeared congested; the alveolar tissue beyond was more or less air-containing, with occasional areas of emphysema.

Under low power, the lumina of some bronchi were filled; others were relatively free. The epithelial walls of the filled bronchi showed extensive infiltration; the submucosa was likewise infiltrated. Here one is dealing with severe endobronchitis and peribronchitis (fig. 2A). Some of the bronchioles showed such a degree of infiltration that they were completely obliterated, endobronchiolitis obliterans (fig. 2B). Endobronchiolitis and peribronchiolitis were pronounced. The capillaries here, as well as those immediately beyond the diseased bronchi, were greatly congested. The areas of most intense infiltration were found between diseased bronchi and large blood vessels. The region adjacent to the opposite wall of such vessels was free from this intense inflammation. The capillary blood appeared normal. Most of the alveoli near the diseased bronchi contained debris or extravasated blood. The alveolar walls which showed the greatest degree of infiltration were those adjacent to diseased bronchi. Midway between such centers of inflammation, the lung tissue appeared more normal, but some of the alveolar walls were exceedingly thin, the alveoli were greatly distended with air, and some had ruptured because of the emphysema.

Under oil immersion, the diseased bronchi revealed a content of desquamated epithelial cells, round cells, polymorphonuclear leukocytes and bacilli which resembled *B. pertussis*. The walls of such bronchi were intensely infiltrated with polymorphonuclear leukocytes and cells of the round type. These cells also appeared in abundance in the submucosa which, like the epithelial wall, in places, was partly obliterated by invading cells. The aforementioned zone of infiltration

which lay between the large blood vessels and the bronchi consisted mainly of cells of the round type. Where the epithelium had desquamated, cells from the submucosa had reached the lumen. Some of the more or less intact cilia were thickly embedded with pertussis-like bacilli. Such bacilli were seen in abundance where



Fig. 2 (Peter K.).—*A*, lung, showing pronounced endobronchitis and peribronchitis, adjacent alveoli (*al*) completely atelectatic and a heavy zone of infiltration (*inf*) about blood vessel (*art*), adjacent to diseased bronchus; ( $\times 160$ ); *B*, two bronchioles (*brle*) separated by capillary (*cap*). The one above is completely obliterated, the one below contains pertussis-like bacilli and cells;  $\times 350$ . *C*, ciliated epithelium of a large bronchus, heavily laden with pertussis-like bacilli. The epithelial structure is obliterated by cell infiltration;  $\times 1,500$ .

tissue changes were most profound (fig. 2C). The endothelium of the capillary walls in the submucosa had proliferated. These capillaries were filled with leukocytes, some of which were passing through the wall toward the diseased bronchioles. The bronchioles showed changes similar to those described for the bronchi. The lumina of completely obliterated bronchioles were filled with plasma cells, mast cells, lymphocytes, polymorphonuclear leukocytes, erythrocytes, pertussis-like bacilli and fibrin (fig. 2B). In some of the patent bronchioles polymorphonuclear leukocytes were abundant. The marked peribronchitis was due to round-cell infiltration. The alveolar walls in these parts were definitely thickened and infiltrated; the alveoli were more or less atelectatic. Some were compressed, others were filled with fresh blood or round cells and polymorphonuclear leukocytes. Pertussis-like bacilli were seen in a number of them.

RHESUS A5.—This young male monkey arrived on Sept. 10, 1927. He weighed 1,600 Gm. The hemoglobin tested 80 per cent. The average leukocyte count for the eighteen days before inoculation was 16,837; the differential blood count was: polymorphonuclears, 48; small lymphocytes, 29; large lymphocytes, 15; eosinophils, 8. Oct. 1, 1927, 1.5 cc. of a two-day growth of *B. pertussis*, strain "Webber," was dropped into the nares. After a week, the animal presented rhinitis, sneezed and coughed. The leukocyte count had reached 59,750; the differential blood count was: polymorphonuclears, 32; small lymphocytes, 57; large lymphocytes, 11. October 10, the nasal and throat cultures were positive for *B. pertussis*; no distemper bacilli were found. The following day, the cough increased in frequency and severity. By October 12, the cough was severe; during one hour, the animal had nine attacks of coughing. October 14, the leukocyte count was 89,400. The animal appeared very ill, and as the percentage of polymorphonuclear leukocytes was increasing, pulmonary involvement was suspected, and the animal was killed for study of the respiratory tract.

The essential postmortem observations were as follows: The lining of the epiglottis, larynx and trachea was pale and pearly white throughout. The lower part of the trachea contained an excess of yellow mucus. *B. pertussis* was found in smears and cultures from the larynx and trachea, but more colonies were obtained from laryngeal mucus. The tracheobronchial lymph glands were somewhat enlarged. Several small, dark red areas were scattered over the posterior part of both lungs, especially in the lower lobe of the right lung. When these areas were cut through, they were found to be consolidated. *B. pertussis* was recovered in smears and cultures from these areas. No other micro-organisms were found. (The recovered bacillus was subsequently inoculated into *Rhesus* A4, which presented a paroxysmal cough seven days later.)

Sections of the larynx showed the ciliated epithelium intact; no lesion was found. Mucus and abundant pertussis-like bacilli were present. In sections of the trachea, many similar bacilli were found on and between the cilia, which appeared intact. The mucus glands did not show involvement, nor did they contain bacilli, despite the fact that many pertussis-like bacilli lined the trachea. No infiltration of the tissues was seen, except in one area which showed superficial necrosis. Here desquamation of the epithelium had occurred, with some infiltration of the submucosa. Pertussis-like bacilli were present in masses on the desquamated epithelium.

Examined with a hand lens, stained sections of the consolidated areas of the lung showed marked infiltration in the immediate vicinity of the bronchi. The largest bronchi contained relatively less debris than did the smaller ones. The density and extent of the infiltration around the bronchi appeared to be in direct proportion to their size.

Under low power, there was marked engorgement of all blood vessels, especially in the region of diseased bronchi. The lumina of some bronchi contained débris, which completely filled some of the smaller ones. The submucosa was thickened and infiltrated, as was also the tissue beyond the elastic layer. There were endobronchitis and marked peribronchitis. About some of the larger bronchi a deeply staining zone of infiltration, greatly thickened in places, surrounded bronchus, cartilage and blood vessels, so that the alveoli appeared completely separated from them. The alveolar tissue in the immediate vicinity of such bronchi showed extensive infiltration, and many of the alveoli appeared completely filled. Farther distant alveoli contained more or less air; some were emphysematous, and the septal walls appeared thickened. Some of the bronchioles showed an intense infiltration with a wide zone of involvement about them. Some of their lumina were filled. Figure 3 shows such a bronchiole (endobronchiolitis and peribronchiolitis).

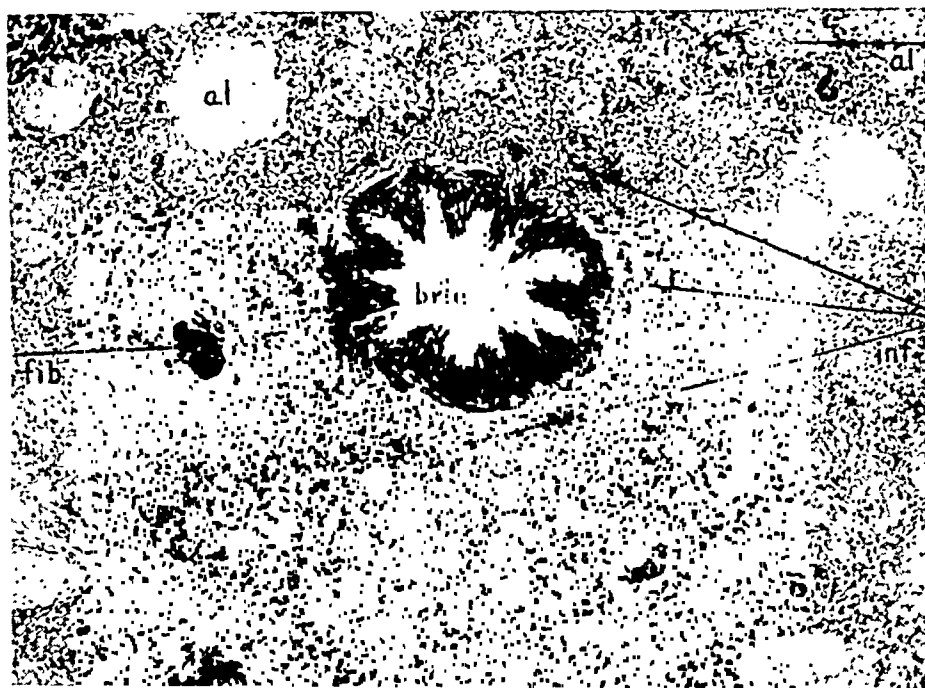


Fig. 3 (Rhesus A5).—Experimental pertussis. A bronchiole (*brlc*) is shown with heavily stained epithelium and infiltrated submucosa (endobronchiolitis and peribronchiolitis);  $\times 70$ .

Under oil immersion, the granular débris in the bronchi consisted of desquamated epithelium, mucus, erythrocytes, polymorphonuclear leukocytes, round cells and pertussis-like bacilli. The columnar cells of the epithelial layer appeared edematous, with the nuclei staining deeply. This layer, on the whole, appeared well intact. In certain areas in which desquamation had occurred, the desquamated cells had become round or cuboidal. There was little cell infiltration of the wall; an occasional polymorphonuclear leukocyte, lymphocyte, plasma cell or mast cell could be seen between the cells. In many areas, the cilia appeared normal; in others, they were missing. Pertussis-like organisms were found on and between some of the cilia.

In that part of the submucosa adjacent to the elastic layer, polymorphonuclear leukocytes were abundant, and in certain areas occurred in dense aggregations. Round

cells predominated in the densely infiltrated areas beyond. The epithelial cells of the bronchioles likewise appeared edematous, and the nuclei of the cells stained deeply. There was little cell infiltration of this layer. Some of the cilia of the bronchioles were densely studded with pertussis-like organisms. The infiltration of the submucosa of the bronchioles was due mainly to cells of the round type, with some polymorphonuclear leukocytes present. Most of the alveoli in the areas of infiltration contained leukocytes, round cells, fibrin, pertussis-like bacilli and erythrocytes. The alveolar parenchyma was likewise infiltrated. The congestion of the capillaries and the free blood in the alveoli near the diseased bronchi formed a striking contrast to the more normal tissue at the periphery. No gram-positive organisms were found. Cultures of these parts post mortem revealed only the Bordet bacillus. The numerous, transversely cut capillaries in the alveolar tissue showed markedly infiltrated walls; their lumina were filled with polymorphonuclear leukocytes, erythrocytes and desquamated endothelial cells.

#### COMMENT

If a susceptible child aspirates pertussis bacilli expelled by a coughing patient, the disease may develop after an incubation period of at least a week. A cough-plate, properly exposed during the catarrhal or early paroxysmal stage, should show colonies of *B. pertussis* within four days. The "pearls" of bronchial mucus coughed up during this time contain *B. pertussis*, often in nearly a pure state, also leukocytes, lymphocytes and desquamated epithelium. This evidence of injury by the toxin of the causative organism shows that early in the disease the bronchi are involved. The presence of bacilli on and between intact cilia in stained sections of the larynx and trachea without visible tissue changes leads one to suspect that the lesion is farther down the bronchial tree. The not infrequent presence of unique râles (Pospischill <sup>6</sup>) during the catarrhal stage is clinical proof that the seat of the infection is in the lung.

Search for the region that showed the most profound injury in uncomplicated experimental pertussis led to the finer bronchi and bronchioles. The microscopic study of the respiratory tract of monkey R2 (without macroscopic pulmonary involvement) offered strong evidence that the bacilli reached the finer branchings of the bronchial tree. Endobronchitis and peribronchitis were more pronounced than were endobronchiolitis and peribronchiolitis. No pertussis-like organisms were found in the alveoli. In Peter K. and Rhesus A5 who showed macroscopic pulmonary changes there was marked involvement of the bronchi, bronchioles and adjacent alveoli. Pertussis-like bacilli were found in abundance in these areas. Endobronchiolitis and peribronchiolitis were as pronounced as were endobronchitis and peribronchitis. Since the bronchioles showed more involvement than those in R2, and as alveolar involvement occurred only in regions adjacent to diseased bronchi and bronchioles, one infers that the bacilli reach the alveoli by way of the respiratory tract, rather than by way of the blood stream. The peri-

vascular infiltration appears to be a protective reaction (fig. 2A). Cells of the round type—lymphocytes, plasma cells and mast cells—predominate in the areas of most profound injury. The response to the invasion of the lung by *B. pertussis* is more proliferative than inflammatory.

#### SUMMARY

The bronchi (and bronchioles) are the primary seat of infection in uncomplicated, experimental pertussis. Endobronchitis and peribronchitis are more pronounced than are endobronchiolitis and peribronchiolitis. The latter are more pronounced in human pertussis with early bronchopneumonia and in experimental pertussis with early bronchopneumonia. Alveolar involvement occurs by way of the bronchioles. Only pertussis-like bacilli are found on and between the cilia of the finer bronchi and bronchioles in uncomplicated experimental pertussis; in human pertussis bronchopneumonia and in experimental pertussis bronchopneumonia, they are found also in the alveoli. Mucopurulent inflammation is soon replaced by round cell infiltration, which is most pronounced where the injury is most profound.



# General Review

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## THE THYROID GLAND IN HYPERTHYROIDISM\*

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The wide variation in the secretory activities of the thyroid gland in different persons is reflected in the many disease processes now recognized as having their origin in disturbances of the gland's anatomic structure. The contributions (variously estimated from 8,000 to 10,000) devoted to the experimental, clinical and pathologic aspects of the problem of goiter have brought its solution nearer. In general, there is now recognized the specific rôle of the thyroid gland as a regulator of metabolism (catabolism, in particular) in proportion to the output of its hormone and the responsiveness of the tissues to the hormone. There are recognized two definite clinical manifestations, hyposecretion and hypersecretion. There is also evidence of the possible production of a perverted secretion. The former two possible functions have given rise to the many interesting clinical phenomena which have been associated with the variable pathologic changes in the thyroid gland.

Knowledge of the thyroid gland in hypersecretion of its hormone has grown insidiously from the imaginative records of the early physicians, who had no knowledge of its structure or function, to the present more accurate observations.

Early considerations of the clinical manifestations of hyperthyroidism had to do with the effect of thyroid enlargements on respiration. The only comments on the changes in the gland were those casually made in connection with the more accentuated early forms of therapy. Although Paracelsus (sixteenth century) definitely established the relationship between endemic goiter and cretinism, definite knowledge of the thyroid dates from the descriptions of it by Vesalius (1543) and Thomas Wharton (1656) and its later classification as a ductless gland by Haller (1776).

While there are many clinical accounts of the nature and evidences of swellings of the neck in association with cretinism or early unnamed myxedema, there is a striking absence of observations of the clinical manifestations which are now known to indicate hyperthyroidism. That such conditions existed is unquestionable, but the failure to observe some

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\* Submitted for publication, Feb. 20, 1929.

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of the symptoms is not so easily understood. In testimony of their existence in former times, Van Leersum<sup>1</sup> pointed to the characteristic types in some of the paintings of the old Flemish, Dutch and German masters, who often reproduced their models too accurately to hide their physical defects. Bilateral or unilateral symmetrical swellings of the thyroid gland with staring eyes and widened palpebral fissures and lean figures were often vividly portrayed.

To Parry<sup>2</sup> belongs the credit of the association of palpitation of the heart with enlargement of the thyroid. An excerpt from his writing reads as follows: "There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed in that connection by medical writers. The malady to which I allude is enlargement of the thyroid gland. The first case of this coincidence which I witnessed was that of Grace B., a married woman, aged thirty-seven, in the month of August, 1786." Parry's full report indicates that he studied three instances of primary hyperthyroidism and two of so-called secondary hyperthyroidism (in women, aged 40 and 50). He described the glands as large, extending half way up the sternocleidomastoid muscles and lying anterior to the pulsating carotid arteries. One of the gland disorders started as a nodule on the right side, but soon spread over the rest of the gland. The records of these few instances and the meager descriptions of the thyroid glands in them constitute the basis of the present enormous superstructure of clinical, pathologic, experimental and etiologic studies concerning its disturbances.

During the seventy years that followed, innumerable clinical observations were made, among which are those of Graves (1835) and Basedow (1840), who pointed out certain definite characteristic symptoms, so that later the condition was designated, by their names, Graves' or Basedow's disease. During this time, the pathologic anatomy of the thyroid received little attention. Surgical removal, although practiced on animals (Schiff, 1859), when attempted on human beings, ended with disastrous results. Watson<sup>3</sup> is given credit for having done the first surgical removal in a case of exophthalmic goiter, a feat that required daring, since surgical treatment of any form of goiter at that time was condemned because of the serious consequences. Schill (1879) reviewed thirty-four articles in the French, German and English literature. He quoted Briere as stating that extirpation of goiter was carried out twenty-nine times during the period from 1785 to 1845; eleven of the

1. Van Leersum: *Arch. internat. pour l'histoire de la méd. a la geog. méd.* 29:282, 1925.

2. Parry, C. H.: *Collections from the Unpublished Medical Writings*, London, Underwood, 1825, vol. 2, p. 3.

3. Watson: *Edinburgh M. J.* 19:252, 1875.

patients died. Between 1845 and 1871, forty-four cases of operation were reported on; twelve of the patients died. Kicher reported a mortality of 19 per cent. In other clinics, the mortality was as high as 40 per cent (Susskind). The total number of such excisions to 1876 was 162. In most of the reports of instances in which operation was done, only brief mention is made of the pathologic nature of the gland, and the notations were largely the result of preoperative clinical observations. Graves,<sup>4</sup> discussing the disturbances in the thyroid gland in three instances, said that "they (the thyroid glands) are considerably larger than natural." He spoke of a "sudden interstitial effusion of blood into the thyroid," which he regarded as "slightly analogous in structure to the tissues called erectile." He preferred to view the changes as hypertrophies. Among the subsequent descriptive terms occurring in the literature, two probably referred to the hypersecreting thyroid gland, namely, parenchymatous goiter and vascular goiter. This dearth of distinctive study of the anatomic changes in the thyroid was probably due to the confusion resulting from the many opinions as to the etiology summed up by Klose and Helwig<sup>5</sup> as follows:

1. The constitutional theory (von Buschan): There was thought to be a secondary involvement of the thyroid gland.

2. The bulbar theory: The seat of the trouble was thought to be in the medulla oblongata and midbrain.

3. The central theory: Cortical lesions were held responsible.

4. The theory of hyperthyroidism and dysthyroidism: The occurrence of an increased or decreased thyroid secretion was suggested.

5. The theory of hypothyroidism: The thyroid was not thought to be a gland of internal secretion but a filter for the blood poisons; its failure of function led to auto-intoxication.

6. The theory of polyglandular disease: The entire endocrine system was considered to be damaged.

7. The sympathetic theory: The disturbance was considered to affect the sympathetic nervous system.

Such theories had their adherents who industriously defended them and accordingly directed their attention to the pathologic anatomy of the organs and tissues concerned. The pathologic anatomy of thyroid enlargements, in general, and those changes underlying exophthalmic goiter, in particular, were touched on only in scattered statements included in clinical dissertations in which the etiology, symptomatology and therapy received the most attention. Pathologic classifications were largely individual concepts, often specifically including the therapy recommended. One of these by Leveque (1872), recorded by Schill,<sup>6</sup> is

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4. Graves: *Clinical Lectures*, Dublin, Fannin & Company, 1848, p. 150.

5. Klose and Helwig: *Klin. Wchnschr.* **2**:627, 1923.

6. Schill: *Schmidt's Jahrb.* **182**:177, 1879.

of interest because of the evidence contained therein of the early use of iodine. Leveque's classification was as follows: "1. Parenchymatous goiter—Iodine internally and externally, iodine injections. 2. Fibrose goiter—Iodine injections, hair setons. 3. Colloid goiter—Iodine internally and externally, hair setons. 4. Cystic goiter—Puncture, drainage, hair setons. 5. Vascular goiter—Chloride of iron injections."

A greater impetus was given the study of the changes in the thyroid (1) by such experiences as that of Kocher (1883),<sup>7</sup> in which he removed the entire organ in exophthalmic goiter and found it to be vital, the removal resulting in "cachexia thyreopriva"; (2) by the experimental prevention of such a condition by the use of thyroid grafts or the administration of thyroid substances (Schiff); (3) by the theory definitely advanced by Möbius<sup>8</sup> that "Graves' disease is an intoxication of the body by a morbid activity of the thyroid gland."

Clinical and pathologic studies now began to include more detailed descriptions of the anatomic changes in the thyroid gland, the former discussions of which were often incidental to dissertations on the pathologic anatomy of other organs and tissues believed at that time to be primarily basic in the production of the symptoms of exophthalmic goiter. In the light of the contribution of Möbius, various gross characteristics of the morbid anatomy were pointed out. Clark<sup>9</sup> spoke of a diffuse primary hypertrophy followed by a shrinking of the gland after death. He described the gland as firm, vascular and fleshy. Bogrow<sup>10</sup> and Baldwin,<sup>11</sup> who made similar observations, also concluded that there was a primary hypertrophy followed by a secondary atrophy. Such diffuse enlargements were confirmed in a general discussion lead by Murray<sup>12</sup> and others.<sup>12</sup> Askanazy,<sup>13</sup> Booth,<sup>14</sup> and Dinkler<sup>15</sup> pointed to the greater frequency of enlargement and involvement of the right lobe, a condition which had been observed many times before in earlier accounts. Hämig<sup>16</sup> discussed instances of massive involvement with diffuse accumulations of colloid. Other similar observations of colloid states were recorded in numerous surgical and postmortem studies of the glands. Notable among such observations is that quoted by Simmonds,<sup>17</sup> who said that while deficiency of colloid of the thyroid

7. Kocher: *Arch. f. klin. Chir.* **29**:254, 1883.

8. Möbius: *Centralbl. f. Nervenhe. u. Psychiat.* **10**:25, 1887.

9. Clark: *Bristol Med.-Chir. J.* **5**:17, 1887.

10. Bogrow: *Neurol. Centralbl.* **14**:13, 1895.

11. Baldwin: *Lancet* **1**:145, 1895.

12. Murray: *Brit. M. J.* **2**:893, 1896.

13. Askanazy: *Arch. f. klin. Med.* **1**:118, 1898.

14. Booth: *New York M. Rec.* **54**:217, 1898.

15. Dinkler: *Arch. f. Psychiat.* **33**:2, 1900.

16. Hämig: *Arch. f. klin. Chir.* **55**:1, 1897.

17. Simmonds: *Schmidt's Jahrb.* **234**:134, 1892.

gland was the rule, not infrequently it was of normal or increased colloid content. These conclusions were in opposition to the views by Farner,<sup>18</sup> Müller,<sup>19</sup> Edmunds,<sup>20</sup> Kraus,<sup>21</sup> Sallerier<sup>22</sup> and Haskovec.<sup>23</sup> These authors were in agreement with the prevailing conception, namely, that the thyroid of "exophthalmic goiter" manifests itself as a compact, fleshy, vascular, granular, colloid-deficient gland, usually with a diffuse involvement. In addition to such changes nodules and cysts were reported found in the glands in scattered instances.

Microscopic changes varied with the gross observations. In general, it was observed that there was a widening out of the acini with a marked tendency to papillary formation, a columnar type of epithelium, a diminution in the colloid, a relative reduction in the supportive connective tissue, an infiltration with round cells and an increased vascularity with engorgement. Those who observed a richness of colloid contended that this substance predominated. Simmonds,<sup>17</sup> who opposed this latter view, stated that he observed a change in the staining of the colloid in two thirds of his cases, a papillomatous hyperplasia in half of them and desquamation in one fourth. He concluded that the irregularity was functional and not bound to any anatomic type. Hezel<sup>24</sup> pointed out that the process could not be considered hyperplastic, but must be viewed as adenomatous. The vascularity, the infiltrations with round cells and the necrotic areas appeared to him as an inflammatory process. Ehrich<sup>25</sup> observed a spotty formation of mucin in newly formed acini. Horsley<sup>26</sup> noted the formation of secretory vacuoles in the epithelial cells. In those glands in which he observed nodular and cystic changes, he found deposits of lime salts and fibrosis.

Möbius,<sup>27</sup> in his monograph on "Die Basedowische Krankheit," summarized his observations on the pathologic anatomy of the thyroid previous to 1900 as follows: "It appears that Basedow's symptoms may be observed in all types of goiter, large and small, hard and soft, with and without cysts and probably in malignant tumors of the gland." He remarked further that if a normal gland existed prior to the onset of the disease, a soft goiter of moderate size, usually larger on the right than on the left side, resulted. The other gross and microscopic changes he regarded as preexisting structures to which the changes induced by

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18. Farner: *Arch. f. path. Anat.* **143**:509, 1896.

19. Müller: *Beitr. z. path. Anat. u. z. allg. Path.* **19**:127, 1896.

20. Edmunds: *J. Path. & Bact.* **3**:488, 1894.

21. Kraus: *Buffalo M. J.* **35**:793, 1896.

22. Sallerier: *Thèse de Paris* **255**:138, 1897.

23. Haskovec: *Schmidt's Jahrb.* **258**:127, 1898.

24. Hezel: *Deutsche Ztschr. f. Nervenhe.* **4**:4, 1893.

25. Ehrich: *Beitr. z. klin. Chir.* **28**:1, 1900.

26. Horsley: *Brit. M. J.* **2**:1623, 1896.

27. Möbius: *Specielle Path. u. Therap., Nothnagel* **22**:18, 1896.

exophthalmic goiter were added. During the next twelve years painstaking experimental, clinical and anatomic studies of goiter, in general, tended firmly to establish the basic rôle of the thyroid in hyperthyroidism. Adherents of the "neurogenic theory" of the causation of exophthalmic goiter continued occasionally to advance pathologic evidence in support of their convictions, but their dissertations failed to stem the tide of studies concerning the relationship of disorders of the thyroid to clinical phenomena associated with its hypersecretion. A greater attempt was made to analyze the different clinical types and to correlate them with pathologic changes in the thyroid. Kocher<sup>28</sup> divided the instances (seventy-nine) in which operation was performed in the clinic of Kocher into the following groups: thirty-seven, high grade exophthalmic goiter; twenty-two, definite exophthalmic goiter with some symptoms missing; fourteen, strumae vasculosae; two, pseudo-exophthalmic goiter, and four, unclassified. In all of these instances the glands were enlarged. The older ones were more firm. Variable types of structure with no marked colloid or nodular types were found grossly and microscopically. Murray,<sup>29</sup> in citing his observations in a number of instances, mentioned four in which hyperthyroidism occurred in the presence of unilateral enlargement with adenoma or cystadenoma.

Histologic studies of the various types of glands in hyperthyroidism now began to be especially emphasized, since up to this time many of the gross characteristics had been more widely observed. Erdheim<sup>30</sup> reviewed and analyzed the more important studies and quoted the following authors and their concepts: (1) Brissand, a thyroid affected but without specific change; (2) Müller, specific cell hyperplasia and stroma, but still a colloid struma; (3) Farner, long follicles, papillary growth and cylindric epithelium; (4) Hämig, parenchymatous hyperplasia, solid cell masses, enlarged follicles and a colloid type in which the typical hyperplasia could not occur; (5) Askanazy, Hämig's effect of colloid, desquamation of cells and an excessive accumulation of connective tissue that shut off the lymphatic drainage and forced the "unripe poisonous thyromucin into blood vessels"; (6) Ehrich, an adherent of the vasoneural theory—a papillary structure to be regarded, as a phenomenon of coalescence, and (7) Langhans, irregularity of epithelium as the most important observation, possibly an increase, decrease or modification of colloid and probably a chemical alteration of secretion. Erdheim in a detailed careful study of a number of glands laid stress on the necessity of differentiating the young from the old cells by a method involving the staining of fat granules with osmium tetroxide, a

28. Kocher, Albert: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **9**:1, 1902.

29. Murray: *Lancet* **2**:1194, 1902.

30. Erdheim: *Beitr. z. path. Anat. u. z. allg. Path.* **33**:158, 1903.

technic which he had previously applied in differentiating adenoma from adenocarcinoma. He concluded (1) that in definite exophthalmic goiter there is a lively development of new formations, (2) that the new follicles may be large with papillae or small with flattened walls, (3) that many of the small cell masses are old and represent follicles that have degenerated through desquamation, (4) that different types of cells may be found in other types of struma, but in exophthalmic goiter the cells are young as determined by the granules, (5) that in addition to these typical changes follicles in which the colloid has degenerated and cysts may occur and (6) that the presence of fat cells in the supportive stroma is physiologic and not alone a matter of nutrition. He thought that the retrogressive changes probably indicate that the increased activity is superimposed on previous disturbances of the thyroid.

Wilson<sup>31</sup> in a clinicopathologic study of 294 instances (operations and autopsies) divided them into two series with four groups in each. In the first series, he included all those types that were regarded as having the initial disturbance in the thyroid, as follows:

1. Eleven cases. The patients were young women with symptoms of from two months' to two years' duration. The thyroid glands were hard and granular and of an average weight of about 30 Gm. The cut surfaces were dry, granular and vascular. Microscopically, the chief characteristics seen in all of them were an increased number of cells with reduplication and a small amount of noneosin-staining secretion.

2. Nine cases. The patients were females, and all presented the classic symptoms. The glands weighed, on the average, about 53 Gm., and were hard, nodular and granular. Microscopically, the chief changes were papillary formations, infolding, large interalveolar increase of parenchyma and large amounts of noneosin-staining substance.

3. Fourteen cases. The patients were females and had had the symptoms for from three to thirty years. The essential microscopic characteristics were large intra-alveolar increase of parenchyma with a greater number of cells in a single layer, reduplication of layers and a large amount of thin secretion.

4. Thirty-four cases. All of these were regarded as in the second and third clinical stages. The essential histologic changes were an increase of stroma, an old intra-alveolar increase of parenchyma, the remains of infolding and a large amount of eosin-staining secretion.

In the second series, secondary changes in the gland were observed. Wilson concluded that the symptoms of exophthalmic goiter are asso-

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31. Wilson: *Am. J. M. Sc.* **136**:851, 1908.

ciated with an increased absorption of an increased secretion; that the larger the number of functioning cells, the greater the secretion; that the more fluid the secretion, the more readily is it absorbed; that dense colloid is probably no evidence of present secretion but the complement of the absorbed portion, and further, that there was evidence of blocked absorption.

Shepherd and Duval,<sup>32</sup> in a study of fifty-nine cases, concluded that no etiologic changes could be regarded as specific for any special type of disease of the thyroid gland. Beck<sup>33</sup> presented another view stating that in simple goiter there is an abnormal increase of normal thyroid tissue and that hypertrophy may be either nodular, diffuse, parenchymatous, colloid, fibrous or vascular. He explained the increased activity on the basis of multiplication of the follicles, an increase of their contents and an associated increase in their vascularity.

Simmonds,<sup>34</sup> in a study of 100 instances of exophthalmic goiter, commented on the minute structural changes as follows: The colloid was diminished in two thirds of the specimens and normal or increased in the remainder. Follicular papillary epithelial hyperplasia and polymorphism of the alveoli were found in one half of the number. The presence of this change he regarded as diagnostic, the absence as of no significance. Desquamation of the epithelium was present in one fourth of the specimens, but this also occurred in acute infections. The hyperplasia of the lymphoid follicles (in 80 per cent of the cases) was a true response to a pathologic secretion; it was not of the inflammatory type. In the 80 per cent of the instances in which it was found, 84 per cent of the patients had symptoms of typical exophthalmic goiter while the other 16 per cent presented an atypical symptomatology. Simmonds further concluded that exophthalmic goiter is a symptom complex with no fixed pathologic picture in the thyroid gland.

While these careful observations were analytic, they did not satisfy the constant demand for a more accurately utilizable classification. Marine and Lenhart<sup>35</sup> attempted this in an interpretation of the structural changes in the hyperplasias of the thyroid. These authors divided such conditions into primary and secondary manifestations, as follows:

Primary (seventeen cases): (A) Developmental Stage: Grossly, in the classic type, the gland was larger, softer and a brighter red. Microscopically, it showed a lessening of the stainable colloid, vacuolization resulting in a granular débris and the formation of high cuboidal epithelium. Later, the gland became gray-red and finally

32. Shepherd and Duval: *Tr. Am. Surg. A.* **27**:56, 1909.

33. Beck: *New York M. J.* **91**:937, 1910.

34. Simmonds: *Deutsche med. Wchnschr.* **37**:2164, 1911.

35. Marine and Lenhardt: *Pathological Anatomy of Exophthalmic Goiter*, *Arch. Int. Med.* **8**:265 (Sept.) 1911.



changed from soft gray-red to grayish opaque, with infolding and increase of connective tissue as the cytologic changes. The glands remained symmetrical and rarely exceeded 200 Gm. in weight. (B) Involutionary Recovery or Colloid Stage: The gross and microscopic changes consisted of a reversal of those observed in group A. (C) The Stage of Exhaustion or Premature Atrophy: Grossly, the gland was smaller and firmer to the touch, granular and of a reddish opacity. The vascular increase remained. The increase of stroma was evident with false lobulation, but colloid was not seen. Microscopically, the acini were pressed by the increase in the connective tissue, with cell masses included. The epithelium was of a uniform high columnar type with a failure to form follicles. Desquamation, hyperchromatic nuclei and mitotic figures were also noted. In comment on the general changes in primary hyperplasia, Marine and Lenhardt pointed out that "the thyroid undergoes exceedingly rapid changes within the limits of health and disease, and further that excessive hyperplasia with hypersecretion unchecked will lead to cell death and in the end-stage to myxedema, and (in children) to developing cretinism with the clinical replacement of the symptoms of exophthalmic goiter by those of myxedema."

In the group of the secondary hyperplasias (twenty-six cases) were placed the active hyperplasias that were thought to have developed from a colloid gland. The essential anatomic changes were similar to those of the primary hyperplasias. Another group presented evidence of hemorrhage, degenerations, tumors and cystic formations, all of which the authors concluded, may modify the adjacent tissues. The stage of exhaustion was similar to that of the first stage in the primary hyperplasia. The pathologic changes described by Marine and Lenhardt were similar to those mentioned briefly by Kocher,<sup>36</sup> who attempted to correlate the exact clinical symptomatology with the cytologic changes and the iodine content of the gland.

Plummer<sup>37</sup> began to evaluate the mass of data that had accumulated, and from studies of his own concluded that exophthalmic goiter is a definite clinical complex associated with a hyperplasia of the thyroid gland that is proportionate to the degree of toxicity (toxic hyperplastic), and that it should be sharply differentiated from the constitutional states that may develop with nonhyperplastic goiter. Wilson<sup>38</sup> corroborated the opinion of Plummer in a detailed study of the thyroid in these different conditions. He also pointed out that many mild cases of toxic goiter reported in the literature have apparently been classed as simple goiter. Wilson further mentioned two divisions of such milder types, namely, class I, hypertrophies, hyperplasias and

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36. Kocher, A.: *Arch. f. klin. Chir.* **95**:1007, 1911.

37. Plummer: *Am. J. M. Sc.* **146**:790, 1913.

38. Wilson: *Tr. A. Am. Phys.* **28**:576, 1913.

regenerations (79 per cent); and class II, fetal and colloid adenomas, adenomatoses and simple colloid goiter (21 per cent). The degree of toxicity could be determined, according to Wilson, from the structural changes with 80 per cent accuracy. Thus, in the numerous records of these investigations there were being slowly evolved criteria of the basic changes in hypersecreting or malsecreting thyroid glands in persons with variable symptoms.

Warthin,<sup>39</sup> in a recent report on 976 resected glands, 30 glands taken at autopsy from patients who had died following operation for exophthalmic goiter and 1,000 thyroid glands from autopsies on other persons, called attention to the existence of lymphoid tissue in connection with the many different structural changes of the thyroid gland in exophthalmic goiter. He concluded that the thymicolymphatic constitution underlies every case of exophthalmic goiter.

When one reflects on the great number of articles that have contributed to knowledge of the pathologic anatomy of the thyroid associated with its hyperactivity, one finds that there has developed a rather definite clinical picture and concept of the gross and microscopic aspects of the so-called classic type of thyroid in exophthalmic goiter. There is a uniformity of supporting evidence that: (1) the gland may vary in size from a very slight to a moderate degree; (2) it is symmetrically enlarged, with the possibility of the right lobe being somewhat larger than the left; (3) there is little accentuation of the lobular markings; (4) the capsule and supportive stroma are little, if at all, increased, (5) the structure of the gland may be vascular or ischemic, if the hyperplasia is marked, (6) the colloid is not grossly visible, (7) the color ranges from pinkish to opaque gray, depending on the intensity of the hyperplasia and the relative vascularity of the gland and (8) it is fleshy and moderately firm. Microscopically, there is observed: (1) a patchy increase in the fibrous connective tissue of the supportive stroma, (2) engorgement of the arteries and veins and dilatation of the lymphatic channels, (3) a variable infiltration with round cells, (4) polymorphism of the alveoli, (5) hyperplasia of the epithelium and hypertrophy with variable infolding and (6) diminution of the colloid with variation in its character. Although there have been many conflicts of opinion as to the significance and value of these different gross and microscopic manifestations, there is an obvious unanimity of the understanding of this specific response of the thyroid in the excess fabrication of its essential substance.

In addition, there has also been evolved another mass of convincing evidence that the thyroid gland does not always respond to stimuli in

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39. Warthin: *Ann. Int. Med.* 2:553, 1928.

this typical classic manner. The citations from the literature to this point indicate that normally the thyroid has a fluctuating physiologic response, the imprints of which may be left in the form of accidental structural modifications that react differently to subsequent stimuli. Under such conditions, a markedly variable clinical and structural response might be expected. Almost paralleling the records of classic examples of exophthalmic goiter are those of atypical manifestations. Interesting studies had been made, and more were to follow in the next thirteen years.

The recognition by Oswald (1899, 1908, 1909) that the activity of the thyroid is confined to its iodine-containing colloid, thyroglobulin, eventually led to the discovery of thyroxin by Kendall (1914). Following this, pertinent observations were made by Plummer,<sup>40</sup> whose presentation of the clinical differentiation between exophthalmic goiter and adenoma with hyperthyroidism served as a stimulus to further segregation of clinical types and the study of the pathologic anatomy of the thyroid gland underlying them. Plummer recorded the following facts as important: 1. There is a previous enlargement in cases of adenoma of the thyroid. 2. The time elapsing between the enlargement and the onset is fourteen and a half years in instances with adenoma and only nine tenths of a year in cases of exophthalmic goiter. 3. Exophthalmos is absent in hyperthyroidism from adenoma. 4. Hypertension and myocardial disease is more frequent in cases of adenoma. 5. Seventy-seven per cent of the patients with adenoma are more than 40 years of age, while those with exophthalmic goiter average 35 years of age. 6. The basal metabolic rate drops rapidly after the removal of an adenoma and slowly after the removal of the thyroid tissue in exophthalmic goiter.

In 1916, Goetsch,<sup>41</sup> who regarded adenoma as a new growth of benign nature with colloid, cystic and fetal types, studied these types with a view to establishing their rôle in the production of toxic symptoms. Employing the technic of Bensley,<sup>42</sup> he observed that the adenomas contained more mitochondria than could be found in the surrounding tissue; and as further evidence of their ability to hypersecrete, he recorded the abatement of symptoms following their surgical removal. Lahey<sup>43</sup> agreed with Goetsch, concluding that while nearly all the cells of the gland took part in the activity of the primary hyperthyroidism, only those in the adenoma were active in secondary hyperthyroidism. In the succeeding years, much clinical and pathologic evidence of the

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40. Plummer: Clinical and Pathologic Relationships of Hyperplastic and Nonhyperplastic Goiter, *J. A. M. A.* **61**:650 (Aug. 30) 1913.

41. Goetsch: *Bull. Johns Hopkins Hosp.* **27**:129, 1916.

42. Bensley: *Am. J. Anat.* **19**:37, 1916.

43. Lahey: *Internat. Clinics* **4**:65, 1917.

rôle of adenoma was recorded in the literature. Jackson<sup>44</sup> observed instances of toxicity with multiple adenoma in the glands. Wilson<sup>45</sup> discussed "nodular goiters" with and without symptoms of hyperthyroidism. He divided them into two groups according to the basal metabolic rate. Shepard<sup>46</sup> was of the opinion that the pathologist is unable to distinguish between an adenoma causing hyperthyroidism and one which is inactive. Hertzler<sup>47</sup> looked on the occurrence of adenoma as an incident in the changing structure of the gland as it progresses through the period of adolescence. He concluded that the whole gland is diseased. Rienhoff<sup>48</sup> in a study of involution or regressive changes divided them into spontaneous involutions and hyperinvolutions. He observed the formation of nodules in regressions of the glands of exophthalmic goiter, and further pointed out that "areas of hyperinvolution correspond clinically and histologically to the so-called colloid adenomas, cystadenomas, fetal and colloid or mixed adenomas and colloid cysts." I<sup>49</sup> observed conditions in adenoma similar to those found by Hertzler and Rienhoff. More recently, Rienhoff and Lewis<sup>50</sup> analyzed 109 instances of nodular goiter with symptoms of hyperthyroidism in comparison with the changes in the remissions of exophthalmic goiters undergoing treatment with iodine. They pointed out that there is a striking similarity in structure between the iodine-treated glands and nodular goiter. They further concluded that "the nodules or involutional bodies are not neoplasms in any sense of the word but are merely regressive sequelae of a previous hypertrophy and hyperplasia of the parenchyma." They further stated that there is no proof of the existence of a hypersecreting neoplasm. Hertzler<sup>51</sup> held similar views; namely, that the diseases of the thyroid gland must be viewed as a continuous process. Thus the nature and origin of these benign so-called adenomas have been discussed at length from the standpoint of the conflicting views of Wolfler,<sup>52</sup> who regarded them as originating in interacinar embryonic cell rests, and that of Virchow, who considered them (except fetal

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44. Jackson: *Wisconsin M. J.* **21**:461, 1923.

45. Wilson: *Am. J. M. Sc.* **165**:738, 1923.

46. Shepard: *California State J. M.* **21**:16, 1923.

47. Hertzler: *Endocrinology* **10**:175, 1926.

48. Rienhoff: *Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter and Their Relation to the Origin of Certain of the So-Called Adenomas*, *Arch. Surg.* **13**:391 (Sept.) 1926.

49. Menne, F. R.: *Northwest Med.* **26**:304, 1927.

50. Rienhoff and Lewis: *Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland*, *Arch. Surg.* **16**:79 (Jan.) 1928.

51. Hertzler: *Pathogenesis of Goiter Considered as One Continuous Disease Process*, *Arch. Surg.* **16**:61 (Jan.) 1928.

52. Wolfler: *Arch. Chir.* **29**:1, 1883.

adenomas) solitary or multiple nodular accumulations originating from a preexisting thyroid pattern. Cline,<sup>53</sup> in a study of 600 instances, concluded that the structural evidence observed by him substantiated the concept of Virchow. Their ability to produce an excess of hormone has never been conclusively proved. Many of the studies seem to indicate that while they may become active and hypersecrete, there is usually enough evidence in the surrounding structure of the gland as a whole to explain the symptoms occurring in a given instance.

During the time that attention was fixed on the importance of nodule formation, allied microscopic structural changes were being analyzed as to their significance in hypersecretion. In 1922, Goetsch<sup>54</sup> called attention to a focal interstitial formation of new acini, which he designated as adenomatosis, and pointed to its being a factor in mild hyperthyroidism. Helwig,<sup>55</sup> in a well illustrated study, pointed to the existence of small, disseminated hyperplasias in the form of interalveolar and intra-alveolar collections of acini with characteristic cellular changes as being responsible for the production of "hyperthyroidisms of the lighter grades." Helwig<sup>56</sup> further traced the steps of development from a simple colloid goiter to a typical exophthalmic type. Holst<sup>57</sup> made similar observations, concluding that changes in primary hyperthyroidism begin as a local proliferation. This further complicated the attempts to establish a definite structural change in the thyroid gland that may be associated with a given clinical picture. One is forced back to the necessity of applying the gross and microscopic criteria of the activity of the thyroid in classic exophthalmic goiter to the many intricate complexities of structure that present themselves for solution. A résumé of the literature leads one to the conclusion that specific clinical classifications of the types of hyperthyroidism are as futile as detailed classifications of the types of nephritis, when one tries to make the whole thyroid gland conform in structure to a fixed set of physiologic irregularities in different persons.

Although there have been conflicting interpretations of the thyroid in health and disease, there are outstanding facts of common observation. It is generally agreed that the gland varies markedly in size and shape and that clinically the picture ranges from cretinism and myxedema to hypersecretion of dysfunction as the case may be. We<sup>58</sup> have been able to group the surgically removed portions or entire glands

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53. Cline: *Am. J. Path.* **1**:235, 1925.

54. Goetsch: *Endocrinology* **6**:59, 1922.

55. Helwig: *Beitr. z. klin. Chir.* **125**:75, 1922.

56. Helwig: *Deutsche med. Wchnschr.* **48**:420, 1922.

57. Holst: *Acta. chir. Scandinav.* **4**:191, 1923.

58. Menne, F. R.; Joyce, and Von Hungen: *Thyroid Disturbances: Clinico-pathologic Study of Three Hundred Instances*, *Arch. Surg.* **13**:329 (Sept.) 1926.

according to their gross pathologic characteristics and predominating microscopic pathologic structures as follows:

- I. Diffuse parenchymatous hyperplasia—marked increased activity
  - (1) Gross observations: Gland compact, vascular or ischemic, grayish to pinkish white and colloid-free
  - (2) Microscopic observations:
    - (a) Hyperplasia and hypertrophy of epithelium
    - (b) Peripheral or general vacuolization of colloid
    - (c) Dilatation of lymph channels and engorgement of blood vessels
    - (d) Variable increase in the supporting stroma with or without round-cell infiltration
- II. Disseminated adenomatous hyperplasia—normal or moderately increased activity or no activity
  - (1) Gross observations: Gland diffusely reddish-brown without noticeable nodularity or accentuation of lobular markings; a variable amount of colloid and pinkish to yellowish gray opacities
  - (2) Microscopic observations:
    - (a) Focal changes similar to those in group I
    - (b) Normal or colloid-distended alveoli
    - (c) Focal hyperplasia and hypertrophy of epithelium
    - (d) Inter-alveolar hillocks or intra-alveolar papillomatous projections
    - (e) Focal collections of round cells or pseudolymphnodes
    - (f) Focally increased vascularity and dilated lymph channels
    - (g) Focal fibrous increase of connective tissue
- III. Nodular adenomatous hyperplasia—subnormal, normal or moderately increased activity
  - (1) Gross observations: Variable nodular accentuation of the lobular markings with or without excessive storage of colloid cystic degeneration, hemorrhage, scarring or deposit of lime salt. The color usually varies with the regressive changes
  - (2) Microscopic observations:
    - (a) Focal changes similar to those found in groups I and II and compensatory
    - (b) Characteristic retrogressive changes
    - (c) Areas of adenomatosis
- IV. Solitary adenoma
  - (1) Gross observations: Adenoma variable in size, circumscribed, solitary or multiple, grayish-white to dark reddish-brown, solid and cystic or colloid-filled. Regressive changes may be present.
  - (2) Microscopic observations:
    - (a) All stages of fetal types of alveoli
    - (b) Peripheral formation of pseudocapsule with round cell infiltration and compressed alveoli
    - (c) Focal hyperactive areas in adjoining parenchyma
    - (d) Adjacent areas of adenomatosis

While the gross division of the portions of the thyroid removed is rather easily affected according to this outline, there are numerous instances of the shading of one group into another. Glands of border line nature may, for the sake of study, be relegated to the group

according to the dominancy of the classifying characteristics. More detailed separations of types of disturbances seem futile.

In the microscopic analysis, it is important to establish histologic criteria of activity or rest. One thing is certain; namely, that the histologic appearance of the gland in group I (diffuse parenchymatous hyperplasia, so-called classic exophthalmic goiter) is just as definite as are the gross and clinical manifestations associated with it. This is conceded to be an entity in all respects. One may therefore safely assume that the microscopic pattern found here is that resulting from the production and delivery of thyroid hormone or its by-products into the lymphatics or veins. There is evidence to show that cellular hypertrophy, hyperplasia, peripheral vacuolization of colloid, dilated lymph channels and veins and the resulting alveolar distortion occur in the order named and are natural steps in the mechanism or function of any ductless gland and that they are accompanied by an increased blood supply to the part. Prolonged activity probably leads to the necessity for more supportive stroma, and the appearance of special inflammatory absorption reactions consisting of collections of lymph cells. Finally, destruction with areas of adenomatosis or a gradual reversal of the process occurs.

Any pathologic classification from a practical point of view is of value only so far as it may be readily fitted into a specific clinical concept. It has been of interest to note that there are many difficulties in such an assorting of thyroid diseases, and that the situation approaches futility when there is an attempt made to give each detail in the morbid anatomy a distinctive entity. Until more exact physiologic knowledge is at hand, the clinician and the pathologist must content themselves with a comparison of the evidences of disease in the patient and the anomalies of thyroid design as seen in the laboratory. The object in presenting this grouping is to show the extreme range of pathologic structure of the thyroid gland that one may find associated with the production of substances leading to so-called hyperthyroidism. In the case of every type represented, the clinical evidences of hyperthyroidism were found. The greater number of instances of classic types were found in the first two groups, but in all the groups were glands of patients who presented all of the typical symptoms of exophthalmic goiter. All gradations from the milder to the more severe forms of hyperthyroidism were found occurring as the result of the types of glands considered.

It seems from the literature that careful cytologic study of any given gland of a patient with clinical evidence of hypersecretion of the thyroid results in the disclosure of minute structural changes adequate to explain the degree of toxicity. Such specific microscopic foci may be entirely masked by the gross retrogressive structural changes of the gland at the time it is removed for study. It furthermore appears

from the conclusions of numerous other investigators that the general trend of opinion conforms to this.

#### THE INFLUENCE OF IODINE ON HYPERSECRETION OF THE THYROID GLAND

After more than a century of familiarity with the isolation and identification of iodine (Coindet, 1820) and a growing knowledge of its natural distribution in plant and animal life, its agency in the physiology of the latter, and of man in particular, is as yet not thoroughly understood.

In the accounts of medical practices of many centuries past are records of the use of iodine-containing substances in many ailments and especially in goiterous enlargements of the neck. Its use in the latter condition gradually became rationalized (1) by the determination of the presence of iodine as a natural constituent of the thyroid gland (Baumann, 1895), (2) by the experiments of Marine and Lenhardt, who protected animals (dogs and fish) from goiterous enlargements by the addition of the required amount of iodine to their food, (3) by the further experiments of these two authors<sup>59</sup> on regeneration and hyperplasia in the thyroid as influenced by iodine, (4) by the isolation and identification of thyroxin as the active principle of the thyroid (Kendall, 1914) and (5) by the observations of Plummer and Boothby concerning its clinical use in hyperactivity. To these might be added many other similar experiments and studies all of which pointed to the specific rôle of iodine in the physiology of the thyroid in health and disease.

While these important advances relative to the identification of iodine as a positive and necessary factor in thyroid functioning were developed, many clinical observations were also made with a view to a better understanding of the empiric use of iodine in thyroid irregularities. As a remedial agent in so-called goiter, iodine had been used in its crude form (ashes of sponge or seaweed) for many thousands of years. The purification of iodine and its compounds led to more accurate dosage and the development of various means of administration. The results were not wholly satisfactory because of the lack of control of clinical conditions and the inability of early clinicians accurately to differentiate the different types of thyroid disease. But from the time of the establishment of exophthalmic goiter (1786) as an entity, it was considered unwise to use iodine in the therapy of this condition. Occasionally, however, on account of erroneous diagnoses or by accident, iodine was administered and beneficial results were noted.

59. Marine and Lenhardt: Relation of Iodin to the Structure of Human Thyroids, *Arch. Int. Med.* 4:440 (Nov.) 1909.



Trousseau<sup>60</sup> (1863), by mistake, gave tincture of iodine instead of tincture of digitalis to a patient with a supposed cardiac irregularity, which was probably secondary to hyperthyroidism. Improvement of the patient was noted and recurrence of the symptoms was observed when the correction was made. Numerous other instances of the beneficial uses of iodine in so-called exophthalmic goiter were recorded, but in general the results were bad, and in many of the large clinics of Europe the use of iodine in this disease fell into disrepute. But surgical removal in primary hyperthyroidism gave a mortality rate so high that frantic efforts were constantly being made to better the technic and to find further aids in the therapy. The introduction of rest in bed, the isolation of clinical types, the use of soporifics and preliminary pole ligations helped appreciably to lower the mortality rate. In the meantime the effect of partial surgical removal on the remaining gland stump was studied by Wagner,<sup>61</sup> Horsley<sup>62</sup> and Halstead,<sup>63</sup> who found that reconstructive hyperplasia and hypertrophy occurred. This observation led to a further understanding of what surgical removal accomplished besides the mass removal of offending parenchyma. It also opened the way for a study of the additional effect of iodine as a therapeutic adjunct.

During the succeeding years many attempts were made to use iodine in instances of hypersecretion, but its effects were too variable and often too dangerous. Its ultimate efficacy was to be dependent on further observations. Kocher<sup>64</sup> referred to the marked reduction of the amount of iodine associated with deficiency of colloid in the glands with marked hyperplasia in hyperthyroidism. Later Marine<sup>65</sup> pointed out that in 137 cases of exophthalmic goiter in which operation or autopsy had been performed, no specific anatomic changes were found; that the iodine content varied directly with the degree of active epithelial hyperplasia; that the administration of iodine in the simple hyperplasias of the thyroid in man and animals is followed in from three to five weeks by a progressive involution of the hyperplasia to its colloid stage. These experiences were confirmed by Kocher and others, who began to observe the effect of the feeding of iodine to exophthalmic patients as having a result that would substantiate this particular influence of iodine. Lowey and Zoudek<sup>66</sup> found that the use of iodine in primary

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60. Trousseau: *Clinical Lectures*, translated by Bazire, London, New Sydenham Society, 1868, vol. 1, p. 587.

61. Wagner: *Wien. med. Bl.* **7**:771, 1884.

62. Horsley: *Lancet* **2**:1163, 1886.

63. Halstead: *Johns Hopkins Hosp. Rep.* **1**:373, 1898.

64. Kocher: *Arch. f. klin. Chir.* **95**:1007, 1911.

65. Marine: *Anatomic and Physiologic Effects of Iodin on the Thyroid Gland of Exophthalmic Goiter*, J. A. M. A. **59**:325 (Aug. 3) 1912.

66. Lowey and Zoudek: *Deutsche med. Wchnschr.* **47**:1387, 1921.

hyperthyroidism tended to bring the basal metabolic rate back to a normal level. Plummer, having in mind the possible toxicity of incompletely iodinated thyroxin and the variations in the symptomatology of the clinical types, suggested that the administration of a compound solution of iodine in instances of primary hyperthyroidism might be of value. Subsequently, Plummer and Boothby<sup>67</sup> published the beneficial results of its use in selected cases. Similar reports by others began to appear. Starr and Segall,<sup>68</sup> in a study of forty-two cases, made additional observations. They determined that the rate of detoxification (based on the reduction per diem in the basal metabolic rate) was 3.7 points, a rate similar to that obtained by Means and Aub<sup>69</sup> with subtotal thyroidectomy alone. They further pointed out that in 48 per cent of these cases, the administration of iodine had the same effect on the basal metabolic rate as the removal of five sixths of the gland; that iodine did not produce permanency of remission, recurrence being the rule, and that the return of intoxication resulted in a much higher basal metabolic rate. They therefore concluded that no gap should be allowed between the therapy employing iodine and the operation. This conclusion was concurred in by Chute,<sup>70</sup> who regarded the "optimal time" for thyroidectomy to be within a period of from two to three weeks after the treatment with iodine was started. During this time he observed the most marked clinical improvements and the greatest drop in the basal metabolic rate. He regarded the operation within such a time limit as safe, and also stressed the fact that the toxicity recurring after cessation of the treatment with iodine is greater than before its use, if surgical removal is not promptly made. He further concluded that in the severe cases iodine reduced the necessity of pole ligations from 51 to 13 per cent, but that iodine, even though administered over a long period of time, does not cure exophthalmic goiter. Petren<sup>71</sup> regarded iodine as having a life-saving action. He also noted that the symptoms reappeared after cessation of the treatment and recommended the use of roentgen rays and ligation as additional measures.

Marie<sup>72</sup> concluded that the results of the use of iodine testify only that a disproportion exists between the iodine content and the requirement of the organism at the time rather than a deficiency of iodine. Marine<sup>73</sup> later called attention to the use of iodine in too large

67. Plummer and Boothby: *J. Iowa M. Soc.* **14**:66, 1924.

68. Starr and Segall: *The Effect of Iodin in Exophthalmic Goiter*, *Arch. Int. Med.* **34**:355 (Sept.) 1924.

69. Means and Aub: *A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism*, *J. A. M. A.* **69**:33 (July 7) 1917.

70. Clute: *The Effect of Compound Solution of Iodin and Rest in Surgery of Exophthalmic Goiter*, *J. A. M. A.* **86**:105 (Jan. 9) 1926.

71. Petren: *Ugesk. f. Laeger.* **88**:363, 1926; abstr., *J. A. M. A.* **87**:72, 1926.

72. Marie: *Presse méd.* **34**:580, 1926.

73. Marine: *Ann. Clin. Med.* **5**:942, 1927.

amounts (compound solution of iodine contains 125 mg. of iodine per cubic centimeters). It was suggested by him that smaller amounts more nearly physiologic (1 mg. daily) should be given. He spoke of the preoperative measure of "heroic doses" as dangerous, from which much harm had occurred and would continue to occur. Marine regarded the beneficial effects of iodine in exophthalmic goiter as limited and its injurious effects as serious. He also stated that these injurious effects had increased during the last three years and were more serious than the disturbances noted as a result of the preventive use of various iodine-containing substances. Marine explained the effect of iodine on the basis of a probable storage of colloid which holds back secretion. He stated that when secretion is released, it is reestablished with full force and yields larger amounts, the gland becoming larger and more solid. Helwig's<sup>74</sup> views were in agreement with those of Marine. He concluded that the feeding of iodine called forth an enlargement of the follicles and a thickening of the colloid, and stated that in his experience the severest cases of exophthalmic goiter were encountered after the administration of iodine.

Sager<sup>75</sup> again called attention to the necessity of differentiating the types of hyperthyroidism before beginning the use of iodine, on the basis of Plummer's views. He quoted Plummer as regarding the action of iodine as due to one of three possibilities: (1) complete iodination of thyroxin in the tissues (possible but improbable); (2) complete iodination of thyroxin in the thyroid (most probable); (3) blocking of the discharge of the hormone.

More definite observations on the structural changes in the thyroid now began to appear (Cattell,<sup>76</sup> Warthin,<sup>77</sup> Giordano,<sup>78</sup> Kaffler,<sup>79</sup> Marine,<sup>80</sup> Helwig,<sup>81</sup> Sager,<sup>75</sup> Rienhoff and Lewis,<sup>80</sup> Menne, Joyce and Stewart<sup>82</sup>). All these studies agree that the essential changes induced by iodine consist of a regression of activities with an accumulation of colloid, a reduction in the degree of hyperplasia and hypertrophy of the epithelium and a decrease in the vascularity. Grossly, the glands tend to become larger, on the average, than untreated glands. The capsule and supportive stroma are not appreciably altered unless considerable

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74. Helwig: *Klin. Wchnschr.* **5**:2356, 1927.

75. Sager: *Exophthalmic Goiter: Pathologic Changes as a Result of the Administration of Iodine (Lugol's Solution)*, *Arch. Surg.* **15**:878 (Dec.) 1927.

76. Cattell: *S. Clin. N. Amer.* **6**:597, 1926.

77. Warthin: *Ann. Clin. Med.* **4**:686, 1926.

78. Giordano, A. S.: *Histologic Changes Following Administration of Iodine in Exophthalmic Goiter*, *Arch. Path.* **1**:881 (June) 1926.

79. Kaffler: *München. med. Wchnschr.* **73**:1400, 1926.

80. Marine: *Ann. Clin. Med.* **5**:942, 1927.

81. Helwig: *Klin. Wchnschr.* **5**:2356, 1927.

82. Menne, Joyce and Stewart: *Ann. Int. Med.* **1**:912, 1928.

time elapses during the therapy. Colloid is visible, and spotty, yellowish gray to pinkish gray opaque areas of hyperplasia may be seen. These changes are not unlike the involutional changes of untreated glands or of the types of disseminated adenomatus hyperplasias associated with hypersecretion. Although clinicians have made an attempt to utilize iodine only in nodule-free glands, occasionally nodules were found in the specimens of glands examined by us. Microscopically, the essential changes noted vary somewhat with the type of disease of the individual gland. In general, there occurs a progressive development of intracinar colloid, an ironing out of the papillary infoldings, a marked reduction in the hyperplasia and hypertrophy of the epithelium and the development of more uniformity in the sizes of the alveoli. As a rule, the longer iodine is administered, the greater is the accumulation of colloid. But over-iodinization in the presence of the continuance of the etiologic factors of the disease not infrequently results in areas of hyperplasia and hypertrophy that break through the colloid resistance, and such areas may then hypersecrete with renewed energy. Because of this limited effect of iodine on the progression of the disease, surgical removal of a large portion of the gland in the hope of a normal rebuilding is still practiced. While the reversion in the pathologic changes of the thyroid gland induced by iodine is valuable from the standpoint of therapy, and throws light on the mechanism of internal secretion in health and in disease, the relationship of iodine to the etiology is still obscure.

#### SUMMARY

The earlier classifications of the pathologic anatomy of the thyroid consisted of extensive lists of anatomic terms indicating different degenerative or retrogressive processes. Such changes were often regarded as disease entities with which certain clinical phenomena could be associated. While there was this confusion in the general knowledge of thyroid irregularities, there was, on the other hand, a more definite concept of the pathologic anatomy of the thyroid in exophthalmic goiter. It is evident from the early literature that the thyroid in such instances usually retains its symmetry, is firm, vascular, free from false lobulation and scant in colloid. Microscopic studies generally agreed on the existence of a patchy increase in the supportive stroma, engorgement of the blood vessels, infiltration with round cells, marked hyperplasia and hypertrophy of the epithelium associated with alveolar distortion and reduction and modification of the colloid. This was the consensus concerning the changes in the gland in hypersecretion.

Observations of atypical gland structure associated with certain if not all the symptoms of hypersecretion gradually began to be recorded. These thyroid glands lacked symmetry; the disturbance was in either one of the lobes, the isthmus, or in the isthmus and one lobe. The patho-

logic changes were markedly variable. In some, the capsule and supportive stroma was particularly increased (interstitial thyroiditis); in others, the anatomic pattern was retained, but spotty pinkish gray areas could be seen in a background moderately rich in colloid. Still others showed a formation of pseudolobules, while others contained solitary or multiple adenomas in various stages of development or retrogression. The recognition of such a wide range of anatomic changes in the thyroid gland and their association with varying grades of hyperactivity served to narrow the division between the definiteness of the structure of the gland in hyperthyroidism, and the many other indefinitely understood structural deformities associated with its diseases. There developed a recognition of the possibility of over-secretion by focal areas often grossly hidden by major distorting pathologic processes in the thyroid.

Solitary adenoma in many of the thyroid glands occurring with symptoms of hyperthyroidism led to the conclusion that such nodules (solitary or multiple) might be responsible for the excessive or atypical production of hormone. Concerning this there developed a conflict of views (1) as to whether such nodules are neoplasms, (2) as to their ability to secrete and (3) as to their effect on the surrounding parenchyma. Glands containing nodules (adenoma?) often presented changes varying from simple unmodified colloid-filled acini to disseminated or diffuse parenchymatous hyperplasias. Accordingly, there has not been advanced any conclusive proof that such nodules are responsible for the toxic symptoms.

The therapeutic influence of iodine on the thyroid gland has been limited to such changes as it may produce in the so-called primary hyperthyroidism. Following its use, the thyroid retains its symmetry, it enlarges somewhat because of the accumulation of colloid, the vascularity is diminished, the hyperplastic areas have a spotty distribution and the colloid become visible. Microscopically, the changes are similar to those that were described previous to the use of iodine as belonging to hyperthyroidism in which disseminated foci of hypertrophy and hyperplasia were found. It has been pointed out that the changes induced by iodine are probably similar to the natural regressive processes of variable activities of thyroid gland in health and in disease. In instances in which patients were erroneously treated on the basis of having nodule-free glands, when one or more nodules really existed, no noteworthy changes were observed within the nodules. But in such cases the characteristic changes induced by iodine were observed in the surrounding affected parenchyma.

A résumé of the many views as to the pathologic anatomic modifications of the thyroid gland associated with modified activity or hyper-

secretion tends to lead to the conclusion that, in addition to the classic changes of primary, fulminating exophthalmic goiter, there are many other grades. It is further apparent that such changes as may be directly concerned with an excessive or imperfect fabrication of hormone may lie hidden or be incompletely evident because of previously formed minor or gross distortions of structure that are contributory to, but not responsible for, the malfunctioning of the thyroid.

## Notes and News

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**University News, Promotions, Resignations, Appointments, Deaths.**—Henry S. K. Willis has been put in charge of the Dows Tuberculosis Research Laboratory at the Johns Hopkins Medical School, succeeding Allen K. Krause, now director of research at the Desert Sanatorium, Tucson, Ariz.

Raymond H. Goodale, formerly professor of pathology in Beirut, has been appointed pathologist to the City Hospital, Worcester, Mass., in the place of Ernst L. Hunt, who has resigned.

Claus W. Jungelblut has resigned as associate professor in bacteriology and experimental pathology at Stanford University to accept a position in the department of bacteriology in the school of medicine of Columbia University, New York.

Alfred Plaut, formerly pathologist at the Woman's Hospital, New York, has accepted the directorship of the laboratory of Beth Israel Hospital, New York.

The death has been announced of Ernest E. Glynn, formerly professor of pathology in the University of Liverpool.

Florence Rena Sabin, member of the Rockefeller Institute for Medical Research, has been given the 1928 Achievement Award (\$5,000) of the Pictorial Review.

**International Congress on Veterinary Medicine.**—The Eleventh International Congress on Veterinary Medicine will be held in London, England, Aug. 4 to 9, 1930. The general secretary is F. Bullock, LL.D., F.C.I.S., 10 Red Lion Square, London, W. C. 1.

**State Cancer Hospital.**—Money has been appropriated for the construction of a state hospital in Atlanta, Ga., for the study and treatment of cancer.

**Laboratory Infection with Coccidioidal Granuloma.**—It is reported that Harold DeLos Chope, assistant in public health and preventive medicine in the school of medicine of Stanford University, San Francisco, has contracted coccidioidal granuloma while working with the fungus of the disease, *Coccidioides immitis*.

**Cancer Research.**—Special gifts for cancer research have been made to the Johns Hopkins Hospital providing for work on the cultivation in vitro of the cancer cell, on a differential stain for the cancer cell, and for research on cancer in the laboratory of surgical pathology.

**Anthropoid Station.**—Yale University has received \$500,000 from the Rockefeller Foundation for the establishment and maintenance for ten years of a station in Florida for the breeding and study of the anthropoid apes. This station will be part of an expanded program in comparative psychobiology, and it will be under the direction of Robert M. Yerkes, professor of psychology at Yale. Pathology is represented on the advisory board by Theobald Smith and H. Gideon Wells.

**Fellowships in Pathology.**—The Charity Hospital, New Orleans, offers two fellowships in pathology, extending over two years from July 1, 1930. The stipend, in addition to full maintenance, is \$900 for the first year and \$1,800 for the second year. These fellowships are open to senior students in accredited medical schools, and applications should be addressed to Dr. Rigney D'Aunoy, Director of the Pathological Department, Charity Hospital, New Orleans.

**The Chicago Medicolegal Society.**—This newly organized society now has about twenty-five members. The president is Paul G. J. Schmitt and the secretary is Eustace L. Benjamin.

**American Society of Clinical Pathologists.**—The ninth annual meeting of this society will be held in Detroit on June 20, 21 and 23, 1930.

# Abstracts from Current Literature

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## Experimental Pathology and Pathologic Physiology

TRANSMISSION OF INTRACRANIAL PRESSURE IN HYDROCEPHALUS IN INFANCY.  
KENNETH D. BLACKFAN, BRONSON CROTHERS and ROBERT N. GANZ, *Am. J. Dis. Child.* **37**:893, 1929.

In infants, the contents of the craniovertebral cavity do not transmit pressure according to the laws governing the pressure relations when fluids completely fill rigid containers.

1. In hydrocephalus, the propagation of abruptly applied pressure of short duration from ventricle to spinal space may be essentially immediate and without decrement. In this case, the probability of widened channels between the two cavities is assumed.

2. Delay in time and decrement in intensity may be noted. This suggests patent though narrow channels. Though there is no evidence on this point, it is suggested that this delay and decrement may also occur in normal infants.

3. The propagation of pressure may be completely blocked. This means, of course, that at the time of reading, at least, a complete discontinuity of pressure exists.

In general, it is believed that the time element in the propagation of pressure is interesting, that it can be graphically recorded and that it is possible that it may be made clinically useful. Certainly, the reliance on isolated measurements of spinal fluid pressure, as indicating intracranial pressures, seems likely to lead to serious error, and the application of the "closed box" theory to infants seems entirely unsound.

AUTHORS' SUMMARY.

DEGENERATION OF THE CEREBRAL CORTEX IN THE COURSE OF PERTUSSIS.  
FRANK R. FORD, *Am. J. Dis. Child.* **37**:1046, 1929.

The history of a child, aged 20 months, who developed cerebral diplegia after pertussis is briefly presented. This was found to be due to a great loss of cortical nerve cells unrelated to vascular disturbances or inflammatory processes. This condition was first described by Husler and Spatz and probably represents the anatomic basis of many of the nervous complications of pertussis. The lesions are different from those which have been found in the nervous system following measles and vaccinia.

AUTHOR'S SUMMARY.

CONGENITAL HEMOLYTIC ICTERUS. J. M. MASTERS, LEON G. ZERFAS and HOWARD B. METTEL, *Am. J. Dis. Child.* **37**:1254, 1929.

Two sisters, aged 5 and 9, with congenital hemolytic icterus were observed for fifteen months before splenectomy without clinical or hematologic evidences of a crisis. Following splenectomy, the red blood cells, hemoglobin content, blood bilirubin and reticulocytes returned to approximately normal levels within a comparatively short time. After splenectomy, the diameter of the red blood cells increased. In the fragility tests, however, the results were unchanged. Eosinophilia was observed in both instances during the postoperative course of the disease.

AUTHORS' SUMMARY.

THE RÔLE OF THE LYMPHATICS IN THE EARLY STAGES OF THE DEVELOPMENT OF OBSTRUCTIVE JAUNDICE. C. MAYO, 2nd, and C. H. GREENE, *Am. J. Physiol.* **89**:280, 1929.

While in dogs it was found that bilirubin and bile acids accumulate rapidly in the blood stream after ligation of the cystic and common ducts, there was an even



more rapid accumulation in the lymph. Drainage of the lymph by a fistula of the thoracic duct delayed the changes in the blood stream but did not prevent the development of jaundice. Ligation of the thoracic duct had less effect than did the establishment of the fistula. The lymph channels appeared to be the most active agents of bile resorption during the first hours of obstructive jaundice.

H. E. EGGERS.

CONGENITAL PYLORIC OBSTRUCTION (AN EXPERIMENTAL STUDY). J. L. BRODIE, *Am. J. Physiol.* **89**:340, 1929.

In rats born of mothers fed on a diet with minimal antineuritic vitamin content, ten of twenty-three showed congenital pyloric obstruction. In those cases in which the obstruction was of lesser degree, or cured by atrophine, polyneuritis later developed. The vagus in all cases examined showed myelin degeneration. This pyloric obstruction was much commoner in young rats of the second generation than in those of the first, and seven eighths of the cases occurred in males. Attention is called to the points of similarity to congenital obstruction in man.

H. E. EGGERS.

ABSORPTION AND EXCRETION OF ARSENIC, BISMUTH AND MERCURY BY THE COLON. A. J. BARGEN, A. E. OSTERBERG and F. C. MANN, *Am. J. Physiol.* **89**:640, 1929.

By the use of an ingenious isolated colonic pocket, the absorption and elimination of arsenic, bismuth and mercury by that organ were studied in the dog. It was found that arsenic in the form of neoarsphenamine was readily absorbed from the colon; there was no evidence of absorption of this compound or of a product similar to acetarsone here. Bismuth in the form of sodium tetra-bismuth-tartrate was both absorbed and excreted. Mercury as mercurochrome was not absorbed; nor was it excreted when administered as mercurochrome or diacetoxymercuri-4-nitro-2-cresol, at least for four hours after its intravenous injection. The colonic lesions following the intravenous injection of mercurials the writers believe can be best explained by local irritation, since there is definite evidence of the elimination of these drugs elsewhere in the gastro-intestinal tract.

H. E. EGGERS.

THE METABOLISM IN CHRONIC ARTHRITIS. L. T. SWAIM, J. A. M. A. **93**:259, 1929.

It appears that in arthritis the metabolic rate is reduced, especially in the early stages. A low rate may be a pre-arthritic sign.

INHERITABLE ANHIDROSIS AND ANADONTIA. ELMER ROBERTS, J. A. M. A. **93**:277, 1929.

The pedigree is given of six generations of a family illustrating this abnormality which appears to be sex-linked.

HYPERPARATHYROIDISM. JULIAN D. BOYD, J. E. MILGRAM and G. STEARNS, J. A. M. A. **93**:684, 1929.

Clinical hyperparathyroidism may give rise to functional impairment of the gastro-intestinal, renal, osseous and muscular systems. It causes excessive elimination of calcium salts in the urine, with increase of the serum calcium concentration. The bone salts are mobilized, and varied types of bone dystrophy may result; while most instances have been representative of osteitis fibrosa generalisata, some lesions have been histologically indistinguishable from giant cell tumors. The characteristics of the urine may simulate those of renal insufficiency. The clinical and laboratory data have led to exploration of the parathyroids in four instances, and in each the removal of a parathyroid adenoma has resulted in relief of symptoms.

AUTHORS' SUMMARY.

THE PROGRESS OF PHYSIOLOGY. AUGUST KROGH, *Science* **70**:200, 1929.

"I think the time has come when special chairs and laboratories should be established for the physiology of disease, morbid physiology or experimental medicine. The main point is that the leaders of such laboratories should have no regular duties connected with the treatment of patients, but they must have a small number of beds at their disposal for the temporary study of selected cases, and they must, of course, be in close and constant contact with the clinical wards. They must have facilities for studying disease experimentally on animals. Within the field of blood circulation and innervation of blood vessels with which I am personally acquainted, I have had the desirability and even necessity of cooperation with the practical medicine brought home to me again and again. I have learned also that the theoretical problems regarding kidney function require for their solution a close study of clinical cases, and I cannot doubt for a moment that great benefit to patients will ultimately result from such a study. Much can be done in this direction by means of existing facilities, but I anticipate an acceleration of progress from the creation of special chairs as outlined, and I feel sure that the resulting contributions to practical medicine would amply and within a short space of time repay the communities for the initial outlay on such departments and for their maintenance."

THE SUPRARENAL MEDULLA. L. ELANT, *Arch. internat. de méd. expér.* **5**:69, 1929.

The histophysiology and microscopic changes of the suprarenal medulla were studied in mice, rabbits and dogs. The secretory activity of the gland presents a chromaffin reaction which can be changed in intensity by the injection of certain drugs. This change is brought about by influencing the gland's content of proepinephrine, which, in turn, is dependent on a certain equilibrium between assimilation and excretion of epinephrine.

A change in the chromaffin reaction is accompanied by certain histologic manifestations as well as changes in the character of the glandular excretion. Following the injection of strychnine the following picture is presented: preservation of the caliber of the large vessels with dilatation of the capillaries, distention of the intercellular and intracordial spaces, formation of vacuoles at the excretory pole, distinct bipolarity of the medullary cells, enlargement of the vascular zone, marked increase in the size of nuclei, nuclear budding and enlargement of the functioning zone. With diminution in the function of the gland there is decrease in cellular and nuclear volume, effacement of cellular bipolarity, narrowing of the excretory channels and regression of the activity zone. There are also certain changes in intracellular structure.

The effects of injecting insulin, as well as the influence of certain infections, wounds and other pathologic processes, are described and discussed.

PEARL M. ZEEK.

INFLUENCE OF SODIUM PHOSPHATE AND CALCIUM SALTS ON THE EFFICIENCY OF THYROID SUBSTANCES. I. ABELIN, *Biochem. Ztschr.* **199**:72, 1928.

A ductless gland produces more or less of its specific internal secretion. Besides this central regulation there is also a peripheral regulation which is not less important, since it changes the efficiency and not the amount of the internal secretion. Of many other factors in this peripheral regulation, the different foodstuffs play an important rôle. For instance, it is a well known fact that the efficiency of thyroxin is changed by feeding meat or fat.

The influence of inorganic salts, especially of calcium and phosphates, was studied on rats with hyperthyroidism experimentally produced. The administration of phosphates increased the efficiency of the thyroid substances, while that of calcium salts diminished it. A formation of glycogen in the liver can often be observed after doses of potassium carbonate, in spite of feeding thyroid gland. The calcium

salts seem to have a specific influence on thyroxin only, and do not change the efficiency of epinephrine.

An antagonism between thyroid function and excess of calcium is demonstrated and plays perhaps a rôle in the etiology of goiter.

C. A. HELLWIG.

#### STUDIES IN IODINE CONTENT OF NORMAL AND PATHOLOGIC THYROID GLANDS.

G. LUNDE, K. CLOSS and K. WUELFERT, *Biochem. Ztschr.* **206**:248, 1929.

Following the method of von Fellenberg, the iodine content of many normal and diseased thyroid glands was determined. Normal Norwegian glands have an average weight of 24.66 Gm. and a total iodine content of 9.86 mg. The relative iodine content of these normal thyroids is 43 mg. per hundred grams of fresh, and 155.29 mg. of dried gland. The iodine content of nodular goiters without hyperthyroidism varies greatly, but is usually much higher than it is generally believed. In the nodular colloid goiter with hyperthyroidism the iodine content was found to be high: from 14.6 to 122.9 mg. per hundred grams of the fresh gland.

The thyroid gland in exophthalmic goiter is poor in iodine and colloid, but it retains both after administration of a compound solution of iodine.

C. A. HELLWIG.

### Pathologic Anatomy

#### PULMONARY ATELECTASIS. HENRY K. MOHLER, *Am. J. M. Sc.* **177**:507, 1929.

Pulmonary atelectasis not associated with surgical or traumatic conditions occurs more frequently than is generally recognized. Two such cases are reported. The most probable etiology is a mechanical obstruction to the bronchi. The condition has been produced experimentally by injecting into the bronchi of animals material removed from the bronchi of patients suffering from pulmonary atelectasis.

PEARL M. ZEEK.

#### THE ARTIFICIAL PRODUCTION OF PUNCTATE BASOPHILIA AND RETICULATION IN ERYTHROCYTES. W. E. COOKE, *Am. J. M. Sc.* **177**:537, 1929.

Punctate basophilia, diffuse polychromasia and reticulation may be produced in any erythrocyte by treatment with benzidine in alcohol and hydrogen peroxide. The stainable substance thus formed is not nuclear in character, but is probably a hemoglobin compound. Its presence may indicate increased permeability or a defect in the lipoid envelop of the erythrocyte. There probably is a close relationship between punctate basophilia, diffuse polychromasia and reticulation and immaturity.

PEARL M. ZEEK.

#### CHANGES IN THE EYE IN LEUKEMIA. EGBERT J. BORGESON and HENRY P. WAGENER, *Am. J. M. Sc.* **177**:663, 1929.

The most common retinal picture in all types of leukemia is that of engorged veins associated with hemorrhagic areas and with exudates of deep nodular or superficial cotton-wool type. An irregularly rounded hemorrhagic area with a nodular white center occurring without other retinal lesions usually justifies the diagnosis of acute leukemia. Anemia is an important factor in the causation of retinal lesions in the leukemias. In myelogenous leukemia hemorrhage in the retina is more common than in the skin, subcutaneous tissues and mucous membranes. In lymphatic leukemia the reverse is true.

PEARL M. ZEEK.

CHRONIC BRONCHIECTASIS. EDWARD S. THORPE, JR., *Am. J. M. Sc.* **177**:759, 1929.

The early pathologic changes seen in this condition are slight interstitial and peribronchial fibrosis at the bases with diaphragmatic pleurisy. The bronchi may show slight annular dilatation, infiltration of the mucosa with loss or distortion of glands, and residual secretion of a tenacious, yellowish-green, mucopurulent character. Bronchopneumonia, pertussis and measles are frequent factors in the etiology since they carry infection deep into the framework of the lungs. Disease of the accessory sinuses helps maintain a state of sepsis. It is of urgent therapeutic value, especially in children, to correlate the early pathologic and clinical observations.

PEARL M. ZEEK.

BILATERAL ANEURYSMS OF THE COMMON ILIAC ARTERIES. HENRY JOACHIM and MAX A. GOLDZIEHER, *Am. J. M. Sc.* **177**:849, 1929.

A case is presented of a bilateral aneurysm of the common iliac arteries of arteriosclerotic origin in which syphilis was definitely excluded. The diagnosis was arrived at by palpation of a large pulsating mass in the left lower abdominal quadrant, which increased in size during the period of observation. There are only two similar cases reported in the literature.

AUTHORS' SUMMARY.

PERIARTERITIS NODOSA. G. A. BENNETT and S. A. LEVINE, *Am. J. M. Sc.* **177**:853, 1929.

A typical case is presented of periarteritis nodosa in a man, aged 22, in whom the disease was associated with hypertension and cardiac and renal insufficiency. At autopsy, nodosities were found along the medium sized arteries.

A second case is presented in which the disease was associated with meningitis of an aseptic type. At autopsy almost all of the blood vessels of the body showed typical nodosities.

PEARL M. ZEEK.

THE SIZE OF THE CONSOLIDATED LUNG IN LOBAR PNEUMONIA. P. N. CORYLLOS and GEORGE L. BIRNBAUM, *Am. J. M. Sc.* **178**:15, 1929.

The size of the affected lobes in lobar pneumonia, contrary to the generally accepted opinion, is smaller than that of the healthy lobes. The enlargement of the consolidated lung is only apparent and is due to the collapse of the healthy lung when the thoracic cavity is opened. In order to appreciate the true sizes of the consolidated and healthy lobes it is necessary to clamp the trachea and then to open the chest with only the minimum manipulation of the healthy lobes. The decreased size of the pneumonic lobe, as shown by roentgen and postmortem studies, points to a similar pathogenesis in pneumonia and atelectasis. These points definitely proved for the dog need further confirmation for the human being.

AUTHORS' SUMMARY.

CARCINOMATOUS ABSCESS OF THE LUNG. MAURICE FISHBERG and ELI H. RUBIN, *Am. J. M. Sc.* **178**:20, 1929.

Fifteen cases of primary cancer of the lung are reported in which clinically and at necropsy excavations were found. It appears that in about one third of the cases of neoplastic disease of the lung the neoplasm breaks down, leaving a cavity after the necrotic tissue is eliminated.

It is emphasized that such patients with excavated carcinoma of the lung often present the seemingly typical symptomatology, physical signs and even roentgenoscopic appearance of abscess of the lung. In fact, the simulation of the clinical picture of pulmonary abscess may last for many months. In all instances of apparently primary abscess of the lung of recent onset in elderly persons the possibility of broken-down neoplasm is to be borne in mind.

AUTHORS' SUMMARY.

BRAIN TUMORS IN CHILDHOOD. FREDERIC H. LEAVITT, *Am. J. M. Sc.* **178**: 229, 1929.

Brain tumors occur with relative frequency in infancy and childhood. The ratio of juvenile to adult cases in this series is 1 to 14, and the favorite location is in the cerebellum, occurring in this situation in more than 60 per cent of the cases. The usual types of tumors encountered are the tuberculomas, the congenital tumors and those of the glioma group. Statistics of recent date, compared to those of twenty years ago, show the lessening frequency of the tuberculous growths. The congenital tumors are generally suprasellar lesions and produce symptoms of dyspituitarism. The glioma group preponderate in childhood regarding both number and malignant state. They are the preadolescent tumor and they constitute about 75 per cent of the new growths in preadolescent brains, and 40 per cent of all brain tumors. In childhood they usually occur in the midcerebellar region, arising from the roof of the fourth ventricle and projecting into the vermis. This situation places them in the most critical position to endanger life and to produce an early internal hydrocephalus by pressure on the iter. The "fetal-rest" theory of the genesis of neoplastic growths is supported by the identical occurrence of cerebellar tumors in monozygotic twins, as reported in this article.

AUTHOR'S SUMMARY.

FIBROSARCOMA OF THE THYROID GLAND. W. O. JOHNSON, *Ann. Surg.* **40**:29, 1929.

Two cases of fibrosarcoma of the thyroid gland are reported in which the malignant process followed eighteen and twenty-seven years after the appearance of a nodule in the glandular substance.

RICHARD A. LIFVENDAHL.

PRIMARY HYPERNEPHROMA OF THE LIVER. T. L. RAMSEY, *Ann. Surg.* **40**:41, 1929.

A mass 22 by 15 cm. was removed from the under surface of the right hepatic lobe. The tumor was composed of a connective tissue capsule which was continuous with the liver capsule. The substance had undergone varying degrees of degeneration, and microscopically the cells were similar to those of the adrenal cortex and were arranged in fascicular fashion. The other sites in which adrenal rests are found are reviewed, and the various theories as to the origin of these types of tumors are given.

RICHARD A. LIFVENDAHL.

CUTANEOUS NEUROMA (AN UNUSUAL CASE). W. W. DUEMLING, *Arch. Dermat. & Syph.* **19**:226, 1929.

The case of an unusual, rapidly forming tumor of the skin resembling an enormous keloid is reported. Histologically, the tumor consisted of bundles of medullated nerve fibers. The tumor is classified as a true neuroma of the skin.

AUTHOR'S SUMMARY.

DERMATOMYOSITIS: A CLINICOPATHOLOGIC STUDY. C. DAVISON, *Arch. Dermat. & Syph.* **19**:255, 1929.

The clinical progress of a patient with dermatomyositis of two years' duration is reported. There was marked involvement of all the muscles especially of the

sternocleidomastoid, with a sore throat leading to tonsillectomy, followed by pulmonary abscess and finally death. Typical and classic lesions were demonstrated by the autopsy, also a coexisting status lymphaticus. AUTHOR'S SUMMARY.

GRANULOMA INGUINALE, CULTURE OF THE DONOVAN BODY. M. GAGE, Arch. Dermat. & Syph. **19**:764, 1929.

*Bacillus mucosus* is a secondary invader of granuloma inguinale. Some believe that it simulates the Donovan bodies. After many unsuccessful attempts, Gage isolated in pure culture an organism from a patient with granuloma inguinale. This organism has all the staining qualities and morphologic characteristics displayed by the Donovan bodies in smears from patients. FRANK M. COCHEMS.

PURPURA ANNULARIS TELANGIECTODES (MAJOCCHI'S DISEASE). MOSES SCHOLTZ, Arch. Dermat. & Syph. **19**:769, 1929.

The author adds another report to the sixty-three previously recorded instances of Majocchi's disease. In this patient gonorrhea is believed to be the etiologic factor. The lesions are described and differentiated from angioma serpiginosum, Schamberg's disease and poikiloderma vasculare atrophicans. An opinion is advanced that angioma serpiginosum is a progressive nevoid, capillary proliferation of the skin differentiating it from Majocchi's disease, Schamberg's disease and poikiloderma which are inflammatory angiodermatoses. AUTHOR'S SUMMARY.

LUDWIG'S ANGINA. A. P. C. ASHHURST, Arch. Surg. **18**:2047, 1929.

This is an excellent historical review of this clinical entity, and a discussion of its pathogenesis and treatment. The author points out that the infection in this disease is different from a lymphogenous infection with lymphadenitis in that it is a diffuse, indurative inflammation of the submental tissues not affecting, as a rule, the parotid, submaxillary and sublingual salivary glands. Eighteen cases are presented, in eleven of which the patients gave a definite history indicating that dental infection was the primary source. A discussion of the anatomy of this region, particularly with reference to the fascial planes, shows how the infiltration becomes more or less walled off from invading the glands, but instead infiltrates through the soft tissues and muscles. Experimental injections of dye were used to demonstrate the route by which this infection may spread, and these showed that the dye follows the planes of the fascia and stains some of the muscles. Interestingly enough, this stain did not diffuse appreciably beyond the midline, either in the neck or in the mouth. The mortality is high, and early incision, drainage and treatment are indicated. N. ENZER.

PERIOSTEAL LYMPHATICS. E. CAMPBELL, Arch. Surg. **18**:2099, 1929.

The lymphatics of the periosteum and long bones were studied in embryo pigs and in a human infant who had died during delivery. The method of study was the injection in the former instances of the lymphatics by way of the thoracic duct. This was not successful. In the case of the infant, india ink was slowly injected into the outer layer of the periosteum under low pressure. The ribs, especially the costochondral junction, were most readily accessible and gave best results. Cats and kittens, dogs and rabbits, and infants similar to the first one studied, were used. By this method a lymph plexus was demonstrated in the periosteum and perichondrium at the costochondral junction in some of the animals. This plexus was largely in the outer layer of the periosteum, but was drained by the larger lymphatic vessels that contained valves. The plexus consisted of many small, thin walled, freely communicating vessels, and no valves could be demonstrated in them. The author was unable to demonstrate penetration of this plexus into the cortex of the bone. However, some penetration was noted at the epiphyseal line. N. ENZER.

•CONGENITAL ATRESIA OF THE BILE DUCTS. L. ROSENBERG and G. E. JUDD, Arch. Surg. **18**:2339, 1929.

A lengthy review is made of the case of an infant aged 3 months, on whom congenital atresia of the bile ducts was demonstrated, and in whom the liver showed a diffuse biliary cirrhosis. A review of the literature is given and a differential diagnosis made. The authors point out particularly that the cirrhosis of the liver is present at birth, and is as much a part of the disease as the atresia of the extrahepatic ducts. The spleen was enlarged in this case, and the authors believe that it was due to hyperplasia of the endothelial system.

N. ENZER.

METASTATIC TUMORS OF THE URINARY BLADDER ORIGINATING FROM THE CARCINOMATA OF THE GASTRO-INTESTINAL TRACT. HAROLD B. HERMANN, J. Urol. **22**:257, 1929.

In ten cases of carcinoma of the gastro-intestinal tract in the male, metastasis in the urinary bladder was found but once. In twelve cases of Krukenberg tumors, metastasis was found in the bladder six times. The bladder was involved simultaneously with the tubes and the uterus. The ovaries seem to play a determining rôle in directing metastasis formation to the pelvic organs. In the stage when the ovarian tumor is accompanied by involvement of the pelvic organs, operative treatment is not justified. Bladder symptoms in cases of Krukenberg tumor are due to the carcinomatus infiltration of the bladder.

AUTHOR'S SUMMARY.

STUDIES IN THE DYNAMICS OF HISTOGENESIS: XIV. THE REMITTENT BACK-PRESSURE VECTORS OF MUSCLE ACTION IN JOINT RANGE OF MOBILIZATION DETERMINE THE MATURE PATTERN OF HUMAN CANCELLOUS BONE. EBEN J. CAREY, Radiology **13**:127, 1929.

The architecture of mature cancellous bone at mono-axial, biaxial and triaxial joints is determined by the back-pressure vectors of muscle action in joint range of mobilization and not by the static load of body weight.

During development there is a pressure of differential growth that results in so-called "vegetative bone formation" in addition to that of muscle action. The origin of bone is a stiffening process of confined and richly vascularized mesenchymal cells enclosed by a circumscribed membrane, and involves the accelerated proliferation of cells growing centrifugally in a relatively small volume against a limiting extrinsic centripetal resistance. The interaction of the centrifugal and centripetal factors of differential growth creates intra-embryonic environmental pressure. This is known as the allelocatalytic effect or the mutual acceleration of the growth of cells dividing in a relatively small volume by the catalyst of growth. The failure to produce bone by tissue culture in vitro is due to the facts that the pressure of structural organization has been eliminated, and that the so-called "osteoblast" has been regarded as a self-differentiated cell capable of forming bone regardless of environment. Bone produced by differential growth, such as myositis ossificans, usually undergoes atrophy, when energy of repair is equalized, if no functional pressure is brought to bear on the bone.

Selective focal atrophy of cancellous bone groups in the adult dog may be accomplished experimentally by the local surgical excision of the muscle the back-pressure vectors of which resulted in the structural expression of specific groups of cancellous trabeculae.

During the prenatal development of the femur in the fetal cow there is a relative shortening of the femur sixfold in relation to the weight of the thigh muscle from the 32.5 cm. to the 90 cm. stage, as well as a decrease in femoral volume relative to femoral weight. The femoral weight and density increase in direct proportion to the weight of the thigh muscle. The femur is apparently hammered relatively shorter and more consolidated during the prenatal period by growth

resistances, especially the back-pressure of the developing tonic thigh musculature. The mature skeleton is a pressure meter of muscle pull.

The calcar femorale or femoral spur, in the neck of the human femur, is the objective expression of the confluent back-pressure vectors which are the resultants of the actions, primarily, of the extensor gluteus maximus and flexor iliopsoas muscles of the hip in sustaining body weight in the erect posture.

The osteoblast is a dependent cell that acquires its morphologic attributes by the position it occupies in the developing embryo or zone of repair in the adult: it is a reaction cell adequately nourished, and consolidated by the stimulus of compression of structural organization, during the period of differential growth and functional mature maintenance.

EBEN J. CAREY.

INSULIN FAT ATROPHY A TRAUMATIC ATROPHIC PANNICULITIS. H. AVERY, Brit. M. J. 1:597, 1929.

Fourteen of the twenty-one recorded cases of atrophy of the subcutaneous fat following the injection of insulin occurred in women. The brand of insulin used apparently is no factor in its production but the practice of repeatedly injecting into one region without varying the site evidently leads to its appearance. Dimpling of the skin first appears and is followed by a depression which enlarges in depth and radius and at times involves the muscle. The skin may adhere to the underlying structures, undergoes no gross changes but occasionally has impaired pain, thermal and tactile sensations. Microscopically, infiltrations of lymphocytes and histiocytes have been noted in the region of the cutaneous blood vessels early in the condition and after three years fibrous strands extend from the corium and divide the fat into coarse lobules. Apparently this subcutaneous fat atrophy is not due to the presence of pancreatic lipase in the insulin but is a nonspecific traumatic panniculitis. Injections of insulin, hypertonic dextrose or saline solutions or injections of narcotics by addicts may cause it, and it simulates but is less intense than traumatic fat necrosis of the breast.

GEORGE RUKSTINAT.

THE LYMPHATIC VESSELS OF THE LUNGS AND THE INTRATHORACIC VISCERAL GANGLIA. H. ROUVIÈRE, Ann. d'anat. Path. 6:113, 1929.

The results of a thorough investigation of the pulmonary lymphatics and of the lymph nodes are given.

B. M. FRIED.

HETEROGENEOUS EPITHELIUM IN THE OVARIES OF CHILDREN. S. AKAGI, Arch. f. Gynäk. 134:390, 1928.

Numerous ovaries of children were examined and several small cystic epithelial formations consisting of ciliated cylindric cells, mucus-producing goblet cells or squamous epithelial cells were observed. Only one type of epithelium was usually present in the individual cysts. In cysts lined by ciliated cells or goblet cells ova were seen. But these cysts are not considered as derivatives of granulosa epithelium, but as results of specific congenital anlagen which were present in the granulosa layer of the ovum. The heterogeneous epithelial cells of the ovary originate from corresponding congenital anlagen of Mueller's epithelium.

W. C. HUEPER.

MELANOTIC PIGMENTATION IN AN OVARIAN CYST. A. LIEPELT, Arch. f. Gynäk. 134:496, 1928.

Dark brown, granular pigmentations were seen in the basal portions of high cuboidal epithelial cells lining an ovarian cyst the size of a goose egg. Larger masses of this pigment are found in the adjacent connective tissue. It has here an extracellular location. The pseudomucinous cyst is regarded as a part of a dermoid.

W. C. HUEPER.



INHALATION OF DIFFERENT KINDS OF COAL DUST. HAROLD BORCHARDT, Virchows Arch. f. path. Anat. **271**:366, 1929.

Soot, hard coal and soft coal inhaled by rabbits lead to lesions much similar to those in the lungs of man. Soft coal (Braunkohle) stimulates connective tissue formation most. Real pneumokoniosis was not reproduced.

ALFRED PLAUT.

HISTOLOGY OF GENERALIZED OSTEOPHYTOSIS (OSTEOARTROPATHIE HYPERTROPHIANTE PNEUMIQUE). CURTIS CRUMP, Virchows Arch. f. path. Anat. **271**:467, 1929.

The histology of this disease has never been accurately described. Therefore, 122 sections were taken from the bones of a woman who died with the fully developed picture of Bamberger-Marie's disease caused by an unusually large metastatic carcinoma in the lung. The material included all the bones of the right foot, the fibula, a fragment of the tibia and the ulna. A cambium layer of the periosteum was found practically everywhere although widely varying in thickness. There was no osteophyt without cambium under it; generally the cambium extended much wider than the osteophyt. Osteoblastic layers, however, were often absent. Numerous lymphocytes and a few eosinophil cells were found in the periosteum and sometimes in the adjacent muscle tissue. There were many Sharpey's fibers in the osteophyt. This primary osteophyt consists of fibrous bone, the arrangement of which is mainly caused by the blood vessels and not at all by mechanical functional causes. It may become lamellous bone later, through a process of reconstruction after resorption (Umbau). But in the case described there was no real secondary osteophyt. The deeper layers of the osteophyt and the upper layers of the compact bone become highly porous. The thin trabeculae in this spongy bone are not mere remnants of the original bone substance but rather newly formed thin trabeculae, while the bone itself has been absorbed. The osteophyt may be separated from the bone by a cleft, which is even demonstrable on the x-ray film. The insertions of tendons and muscles are all on this outer tube of osteophyt which more or less completely surrounds the bone. At the points of insertions the osteophyt has been found to be thicker or thinner than in other parts of bone; occasionally it was absent. The cleft later on may be filled by bone. Osteophytic layers of different age can be seen on top of each other. The extreme porosis transforms the compact bone into something similar to a skull bone with thin tabula interna and externa; the thin compacta of the tubular bones of the foot was found completely porotic. During these processes the fatty marrow partly becomes cellular and vascular. Subcortical zones of red marrow are visible on the cut surfaces of the bones. The synovialis contains lymphocytes and some eosinophil cells. In the cartilage some fibrinoid degeneration is found; layers near the joint become clear and show their fibers. A pannus from the periosteum destroys parts of the cartilage, and some destruction is wrought by the bone marrow. Together with the exostoses this gives a picture of arthritis deformans. It is doubtful how far this (toxic?) arthritis is part of the disease in question. Occasionally new cartilage is formed. Under one nail a thin osteophytic layer was found; there was no thickening of the soft parts of the toe tip. It is not certain if this was a true drum stick formation. The histologic examination of the bones and of the other organs, including the glands with internal secretion, revealed nothing about the cause of the disease.

ALFRED PLAUT.

THE HISTOLOGY OF GLANDS OF INTERNAL SECRETION IN CHONDRODYSTROPHIC CHICK EMBRYOS. WALTER LANDAUER, Virchows Arch. f. path. Anat. **271**: 534, 1929.

Thymus thyroid parathyroids and epiphysis of chondrodystrophic chick embryos are retarded in their development and offer no explanation for the disease. In the

anterior lobe of hypophysis the arrangement of follicles is disturbed and the whole organ is much smaller. Perhaps the smallness of the sella turcica is responsible for that.

ALFRED PLAUT.

MORPHOLOGY AND FUNCTION OF THE LYMPHATIC TISSUE. J. WAETJEN, Virchows Arch. f. path. Anat. **271**:556, 1929.

Discussion of the function of the germinal centers is given. They are not the only point at which lymphocytes are formed; on the other hand, it is impossible to deny that lymphocytes are formed in them. If the germinal centers are the seat of normal destruction of lymphocytes, why then are they so numerous and persistent in the tonsils? The formation of germinal centers indicates the presence of a cell-damaging agent. The fact that radiation attacks the germinal centers so easily is consistent with the conception that it is the seat of cell formation. In the question of function of lymph nodes it is especially difficult to draw conclusions from the morphologic pictures.

ALFRED PLAUT.

PROGRESSIVE MULTICENTRIC CYSTIC-PAPILLARY ADENOMATOSIS OF PANCREAS. ROSARIO MARZIANI, Virchows Arch. f. path. Anat. **271**:625, 1929.

The author reports the case of a woman, aged 68. The condition was found accidentally at autopsy. The pancreas, which was normal in length, was partly thickened. On the caput a thin-walled cyst the size of a pigeon's egg and a few smaller cysts were found. The ducts were intact and there was no inflammation or malformation. The etiology was unknown.

ALFRED PLAUT.

DEPOSITS OF LIPOIDS AND OF IRON IN THE SUPRARENAL GLANDS AND TESTICLES OF BOYS. CARL BLUMENSAAT, Virchows Arch. f. path. Anat. **271**:639, 1929.

This study is based on fifty-one autopsies on boys between 1 and 15 years of age. Twelve had died of tuberculosis, eight of diphtheria, six of purulent meningitis, five of pneumonia and five of tumors.

The lipoids in the suprarenal glands decrease during disease just as they do in adults. The lipoids of the germ cells are increased in meningitis only. In the interstitial cells a slight increase was noted in other infectious diseases also.

Up to the age of 5 years lipoids are nearly absent in the germ cells; they slowly increase up to the beginning of puberty. Iron deposits in both organs were unimportant.

ALFRED PLAUT.

### Pathologic Chemistry and Physics

PIGMENT FORMATION. BRUNO BLOCK, Am. J. M. Sc. **177**:609, 1929.

A specific reaction for melanin-forming cells is described. The agent within the cells which is responsible for this reaction has the characteristics of an oxidizing ferment and is probably identical with the natural pigment producing oxydase of the cells. The distribution, localization, characteristics and composition of melanin are discussed.

PEARL M. ZEEK.

CALCIUM AND MAGNESIUM RELATIONS IN THE ANIMAL. W. P. ELMSLIE and H. STEENBOCK, J. Biol. Chem. **82**:611, 1929.

The antagonism manifested between the ions of calcium and magnesium does not appear to be sufficiently pronounced to suggest that the normal calcium balance may be seriously endangered following the ordinary therapeutic administration of a magnesium salt. The addition of an excess of magnesium to the ration of the rat appears to produce no demonstrable effect on the calcium absorption. It does not increase the severity of an already present, rachitic condition. The

selective absorption capacity of the digestive tract apparently represents an adequate protective mechanism for the exclusion of excesses of magnesium.

ARTHUR LOCKE.

ON THE QUESTION OF THE ORIGIN OF URINARY AMMONIA. S. R. BENEDICT and T. P. NASH, JR., J. Biol. Chem. **82**:673, 1929.

Argument is presented for the conception that urinary ammonia is produced within the kidney from urea. Ammonia is regarded as playing no part in the neutralization of acids within the organism, either intracellularly or in the blood stream.

ARTHUR LOCKE.

### Microbiology and Parasitology

THE DEMONSTRATION OF TUBERCLE BACILLI IN SMALL CHILDREN WITH PULMONARY TUBERCULOSIS. V. POULSEN, K. A. JENSEN and E. HUSTED, Am. J. Dis. Child. **37**:900, 1929.

It is difficult to demonstrate the presence of tubercle bacilli in pulmonary tuberculosis in children who are so young that they swallow the expectoration. In view of this fact, Poulsen, Jensen and Husted adopted the following method. In the morning after the child has fasted for about six hours the stomach is washed with from 200 to 300 cc. of sterile water. The wash water is then centrifugated. The sediment is homogenized and stained after Ziehl-Neelsen's method and examined. Cultures are made of the sediment on Petroff's medium and guinea-pigs are also inoculated. A series of fifteen cases was studied, and the microscopic examination showed tubercle bacilli in the majority of cases. In those cases in which the microscopic examination was not positive and in which there were clinical evidences of tuberculosis, the culture and guinea-pig inoculation bore out the diagnosis.

HARRY E. LANDT.

SUMMARY OF INVESTIGATIONS ON THE ETIOLOGY OF TROPICAL SPRUE IN PORTO RICO. C. WEISS, F. LANDRON, O. COSTA-MANDRY and D. WILKES-WEISS, Ann. Int. Med. **2**:1198, 1929.

In a study of eighty-five cases of tropical sprue, the authors found that *Monilia psilosis ashfordi* was present in the feces of the majority of the patients. This fungus could not be recovered from many typical cases, and it was frequently found in the feces of persons not suffering from sprue. Inoculation of human volunteers with scrapings from the tongues of patients with sprue and with cultures of *Monilia psilosis* has given entirely negative results. Attempts to transmit the disease to monkeys by similar inoculations and by feeding the feces of patients with sprue have been equally unsuccessful. Skin tests on patients with sprue and controls with exotoxins and endotoxins of *Monilia psilosis* fail to show an immunologic relationship. The blood of patients with sprue exhibits no monilicidal activity.

The rarity of achlorhydria in sprue is an important point in differentiating the disease from pernicious anemia.

WALTER M. SIMPSON.

TULAREMIA RESEMBLING SPOROTRICHOSIS. B. SHELMIRE, Arch. Dermat. & Syph. **19**:918, 1929.

A patient with tularemia had a cutaneous eruption closely simulating sporotrichosis which could not be excluded on clinical grounds alone. A diagnosis of tularemia was made because of the positive agglutination tests of the patient's blood serum for tularemia, repeated negative cultures for the sporothrix, and the failure of the eruption to respond to potassium iodide by mouth. A clinical feature not in accord with the diagnosis was the subsequent necrosis of the axillary and epitrochlear lymph glands.

AUTHOR'S SUMMARY.

MELITENSIS AND ABORTUS INFECTIONS IN THE UNITED STATES. CHARLES W. WAINWRIGHT, Bull. Johns Hopkins Hosp. 45:133, 1929.

In America, melitensis infection is confined to the goat raising areas, while abortus infection is general and widespread. The disease presumably abortus infection is much more prevalent than the literature would lead one to suspect. Both infections occur in persons of all age periods, but the occurrence of positive agglutinations in infants suggests the possibility that the disease is more common at this age than is supposed. The majority of cases of both types of infection occur in males. Occupation played an important part in the recorded cases of melitensis infection. The incidence of contact infection from handling goats was so high that the disease assumed, in this small series, the proportions of an occupational disease. The high incidence of laboratory infection with the abortus variety entitles this organism, as well as the melitensis variety, to respect on the part of investigators. Fever was by far the most constant symptom of onset. The severity of the symptoms of onset was certainly greater in the cases of melitensis infection. The striking difference in the occurrence of pain in the back of the neck is worthy of note. The results of physical examination were strikingly negative in both series, and little difference could be seen in the objective observations. Constipation was outstanding in the melitensis group, and there was frequently an associated tympanites. Joint pains and swellings of the joints were much more prominent in the cases of melitensis infection, as was the occurrence of orchitis. The occurrence of the abortus variety in an ovarian cyst six years after initial symptoms demonstrates the possibility of latent foci. Records of absence of relapse were found only for the abortus group. Normal or reduced white cell counts predominated in the series. There was a relative mononucleosis in a large percentage of the cases, but no striking variation could be found in the response in either group. The existence of a proagglutinoid zone makes it imperative that all dilutions be made when the agglutination reaction is sought for, else the possibility of having missed the reaction in low dilution will always be present. There is a possibility of the infection existing in the absence of the agglutination reaction in the serum. The organism may be recovered from the blood and urine without agglutinins being demonstrable in the serum. The temperature curve is much more typical in the melitensis infection, although varied temperature curves occur. The comparison of the two infections shows the melitensis infection to be generally more in accord with that described as malta or undulant fever, and this infection is usually more severe than the abortus infection.

AUTHOR'S SUMMARY.

HEMOLYTIC STREPTOCOCCUS GANGRENE. FRANK L. MELENEY, J. A. M. A. 92:2009, 1929.

The disease is a clinical entity that should be readily recognized. The most important clinical characteristics are the rapidity of development; the profound prostration of the patient, and the pathognomonic sign, which is a dusky hue of the skin with or without blisters or bullae and usually appearing on the third, fourth or fifth day. It reminds one of erysipelas, but one recognizes at once that it is not erysipelas. Certain clinical and pathologic characteristics distinguish it from the latter disease. The margin is not raised and usually is not clearly defined. Dark blisters and bullae and dusky skin appear early. The condition differs from ordinary streptococcus cellulitis by the greater rapidity of development, by the rarity of lymphangitis and lymphadenitis and by the early appearance of dusky skin or blisters. In sharp contradistinction to other streptococcus infections, incisions should be made as soon as the condition is diagnosed; for the process will promptly subside if the incisions are adequate and the skin, which is not yet dead, will be preserved. Prompt operation makes all the difference between rapid resolution of the process, on the one hand, and great destruction of tissue, if not metastasis and death, on the other.

AUTHOR'S SUMMARY.

THE FILTRABLE ELEMENTS OF THE TUBERCLE BACILLUS. A. CALMETTE, J. VALTIS and A. SAENZ, J. A. M. A. **92**:2086, 1929.

The authors insist on the existence of filtrable elements derived from the tubercle bacillus. They believe that these elements are invisible.

LIVING MENINGOCOCCI IN SPINAL FLUID TWENTY-SIX HOURS AFTER EMBALMMENT. HUNTINGTON WILLIAMS, R. VAN WOERT and V. W. BERGSTROM, J. A. M. A. **93**:437, 1929.

Live meningococci were isolated from the spinal fluid taken post mortem from an 8 year old child.

The child had died on the fourth day of illness. The body had been embalmed (by the cavity method) for twenty-six hours when the spinal puncture was made.

Thirty hours had elapsed from the time of death until the spinal fluid was examined in the laboratory.

The meningococci did not belong to any particular type, but agglutinated polyvalent antimeningococcus immune serum.

Postmortem spinal puncture has been shown to be of value in differential diagnosis, even after embalmmment has been completed.

AUTHORS' SUMMARY.

ACUTE ASCENDING MYELITIS DUE TO THE VIRUS OF RABIES. RALPH E. KNUTTI, J. A. M. A. **93**:754, 1929.

The case reported is that of an ascending paralysis due to an acute destructive rabic myelitis. The diagnosis is based on the presence of Negri bodies in ganglion cells of the spinal cord, and on the development of rabies in inoculated rabbits. The case reported is believed to be unique in its pathologic anatomy. An attempt should be made to establish the etiologic agent of every case of a similar nature not only by bacteriologic studies but, in those terminating fatally, by inoculation of rabbits and monkeys with spinal cord to establish the presence of rabic, poliomyelitic or other viruses.

AUTHOR'S SUMMARY.

RICKETTSIA-LIKE ORGANISMS IN THE SCROTAL SAC OF GUINEA-PIGS WITH EUROPEAN TYPHUS. HENRY PINKERTON, J. Infect. Dis. **44**:337, 1929.

Guinea-pigs, inoculated intraperitoneally with European typhus, occasionally show a scrotal reaction similar to that seen in Mexican typhus, but much less conspicuous, more transient and rarely demonstrable during life. They almost invariably, at the end of the incubation period, show a gelatinous exudate on the surface of both visceral and parietal layers of the tunica vaginalis.

Rickettsia-like organisms similar to those described by Mooser in Mexican typhus, and probably identical with them, may be found in smears of this exudate. Morphologically and in their staining reactions, these organisms are indistinguishable from those found in smears from the gut of the European typhus louse. These organisms have been absent from control preparations, and have not multiplied in artificial mediums. In European typhus, an organized exudate, free from demonstrable organisms, is frequently found on the surface of the testes on from the third to the fifth days of fever. Previous infection with Mexican typhus protects a guinea-pig against infection with European typhus, and no organisms can be found in smears from the scrotal sac of these guinea-pigs. Guinea-pigs after recovering from European typhus are likewise immune to Mexican typhus. The reaction in the scrotal sac is regarded, in both strains, as the result of a local preliminary multiplication of the virus. In Mexican typhus, this local reaction is much more severe. Otherwise, the two strains show an essential similarity in the guinea-pig, both clinically and pathologically. The organism described in each

strain is in all probability the cause of the disease with which it is associated, and Mexican and European typhus are probably only slightly different strains of the same disease.

AUTHOR'S SUMMARY.

THE VIABILITY OF THE ORGANISM OF ROCKY MOUNTAIN SPOTTED FEVER IN GLYCEROL. ARTHUR G. KING, J. Infect. Dis. **44**:357, 1929.

The experiments of Spencer and Parker showing the viability of the organism of Rocky Mountain spotted fever in glycerol are in part confirmed. This viability is exceedingly variable, however, existing in 100 per cent of cases up to twenty days, and in only 14 per cent of cases in the period from forty to sixty days. There is no outstanding difference between the effect of 100 per cent glycerol and that of 50 per cent glycerol. Complete dehydration does not seem to be essential.

Brain is distinctly the tissue of choice. There is presented a successful means of maintaining the organism of Rocky Mountain spotted fever in the laboratory by inoculating guinea-pigs successively at four week intervals with the brain of the previous guinea-pig stored in glycerol in the cold room.

AUTHOR'S SUMMARY.

ACTIVITY OF HERPETIC VIRUS IN MICE. H. B. ANDERVONT, J. Infect. Dis. **44**:383, 1929.

It is believed that a sufficient number of experiments have been performed to justify the conclusion that, with the technic described, mice react to intracranial inoculation of strong herpetic virus with typical encephalitic symptoms. The possibility that other etiologic agents as described by Lauda and Hamm and Cowdry and Nicholson were responsible for the observed symptoms was eliminated by rabbit tests for the herpetic virus. Studies on the response to other routes of infection have not been completed because it was deemed advisable to do such tests when comparing the susceptibility of mice to a weaker strain of virus. These experiments are now in progress. Forty mouse-brain passages of the JB virus over a period of ten months failed to modify its pathogenicity for the rabbit when tested in the brain, cornea or skin. A series of six intracutaneous inoculations in mice gave rise to a fatal encephalitis and had no apparent attenuating influence on the neurotrophic properties of the strain as determined by the rabbit brain and cornea. These results when compared with those of Flexner, who worked with the same virus, imply that the mouse is more susceptible than the guinea-pig.

The observation that young (14 day old) mice are more sensitive to intracutaneous inoculation of the virus might be offered as a reason for the varying results of other investigators, as noted in the beginning of this paper. This observation is also in harmony with results obtained in ascertaining the susceptibility of young and full-grown chickens to the vaccine virus. The work also suggests the feasibility of utilizing mice as a means of propagating herpetic virus for experimental purposes. It does not, however, as yet justify the employment of the mouse as a regular test animal, since with weaker strains the results might be less consistent.

AUTHOR'S SUMMARY.

ALCALIGENES ORGANISM FROM BLOOD OF THREE PATIENTS WITH GANGRENOUS APPENDICITIS. EMIL WEISS, J. Infect. Dis. **44**:394, 1929.

An organism apparently belonging to the genus *Alcaligenes* was isolated in three instances from blood of patients with gangrenous appendicitis. The name *Alcaligenes appendicilis* is suggested for it.

AUTHOR'S SUMMARY.

THE HEAT RESISTANCE OF BACTERIAL SPORES. O. B. WILLIAMS, J. Infect. Dis. **44**:421, 1929.

Evidence gleaned from the literature and accumulated during the progress of this work supports the idea that the cause of death in cells exposed to a high

temperature is the coagulation of bacterial protein. Conditions which render protein more difficult to coagulate consequently result in an increased resistance to heat. The water and the ash content of the cell appear to be especially important in this connection. However, cultivation under certain nutritive conditions which do not appear to be intimately related to either the water or the ash of the cell has invariably resulted in the production of resistant spores.

AUTHOR'S SUMMARY.

VIRULENCE OF *B. PARATYPHOSUS B* IN WHITE MICE. R. D. FRIEDLANDER and K. F. MEYER, J. Infect. Dis. **44**:466, 1929.

It was found impossible to raise the virulence of a strain *B. aertrycke* for white mice after prolonged passage in the device described by Weiner, either by three or six hour intervals in plain hormone broth or by six hour subcultures in broth containing antiserum for the "rough" type of *B. aertrycke*. The fact that the virulence could not be raised for white mice is explained by the supposition that the strain of *B. aertrycke* was already in a state of maximum virulence for these animals. Finally, the term virulence must be indelibly associated with host-environment, susceptibility and immunity as well as with the invasive powers of any particular organism.

AUTHORS' SUMMARY.

VIRULENCE OF *B. PARATYPHOSUS B* IN GUINEA-PIGS. R. D. FRIEDLANDER and L. D. HERTERT, J. Infect. Dis. **44**:481, 1929.

It was impracticable to increase the virulence of a strain of *B. aertrycke* for guinea-pigs after passage in plain hormone broth at six hour intervals or in rough antiserum broth at six or twenty-four hour intervals.

The inability to raise the virulence of *B. aertrycke* for guinea-pigs is explained by the fact that these animals offer an unfavorable environment for the growth of this organism as evidenced by the absence of antibody response.

AUTHORS' SUMMARY.

SEDIMENTATION RATE OF RED BLOOD CORPUSCLES IN ACUTE AND CHRONIC INFECTIONS. MARGARET E. WYLIE, J. Infect. Dis. **45**:6, 1929.

The method of Zeckwer and Goodell is easily carried out and gives sufficiently accurate results for clinical purposes. The average rate of sedimentation in all the infections studied was definitely below the normal average. The speed of sedimentation of the red cells varied with different infections but it was not possible to make a specific diagnosis by this method.

The phenomenon is not influenced by the age of the patient, nor by the height of the fever per se. It is probable that the rate of sedimentation is determined by the amount of tissue destruction. It is certainly not dependent, in cases of tuberculous infection at least, on the resistance of the patient. The sedimentation rate varies with the general clinical condition, a decrease in the speed of sedimentation indicating improvement.

AUTHOR'S SUMMARY.

THE CYTOLOGY AND MICROCHEMISTRY OF MYCOBACTERIUM TUBERCULOSIS. GEORGES KNAYSJ, J. Infect. Dis. **45**:13, 1929.

The young cell of *Mycobacterium tuberculosis* consists of a membrane presenting thickened areas and granular appendages on its internal surface, which surrounds a very dense, deeply staining cytoplasm permeated by a vacuolar system and inclosing dense, round or oval hyperchromatic granules. The membrane and the granules seem to be made up of similar substances staining metachromatically with dilute old methylene blue solutions (methylthionine chloride, U. S. P.) and taking up iodine and the fat dyes to a great extent. This substance is not removed by boiling in water for one hour, nor by 5 per cent sodium hydroxide, 5 per cent

sulphuric acid, glacial acetic acid or chloroform, at the end of the week. In old cells, the membrane increases in thickness and undergoes, together with the granules, gradual degeneration.

The cell divides by drawing back of the protoplasm and the formation of two closing membranes, without constriction of the mother cell at the zone of division. The granules may divide but they do not seem to be associated constantly with cell division.

The present investigations do not substantiate the assumption of a wax or fat sheath around the cell of the tubercle bacillus or of wax or fat granules inside of the cell.

AUTHOR'S SUMMARY.

COMPARATIVE STUDY OF *BACILLUS SORDELLII* (HALL AND SCOTT) AND *CLOSTRIDIUM OEDEMATOIDES* (MELENEY, HUMPHREYS AND CARP). IVAN C. HALL, MARION REINHARDT RYMER and ERWIN JUNGHIERR, J. Infect. Dis. **45:42**, 1929.

*Bacillus sordellii* and *Clostridium oedematoides* are identical species in all essential morphologic and cultural properties and in their toxin-antitoxin reactions.

AUTHORS' SUMMARY.

THE OCCURRENCE OF NONTOXIC STRAINS OF *CL. PARABOTULINUM*. J. B. GUNNISON and K. F. MEYER, J. Infect. Dis. **45:79**, 1929.

Nontoxic strains which are morphologically, culturally and serologically identical with *Clostridium parobotulinum* have been isolated repeatedly from contaminated food products. The toxic and atoxic elements present in a sample may be considered as variants of the same organism. The three nontoxic strains isolated in this laboratory from home canned corn, home canned Bartlett pears and pickled spiced sardines are agglutinated by antiserums of group 5 type B. Nontoxic cultures of anerobes resembling *Cl. parobotulinum* should not be classified as *Cl. sporogenes* until serologic tests have been made.

AUTHORS' SUMMARY.

COMPARATIVE STUDY OF NONTOXIC AND TOXIC STRAINS OF *CL. PARABOTULINUM*. C. T. TOWNSEND, J. Infect. Dis. **45:87**, 1929.

It is not possible to differentiate toxic from nontoxic strains of *Cl. parobotulinum* by the usual cultural, biochemical and serologic methods.

AUTHOR'S SUMMARY.

EUROPEAN STRAINS OF *CL. BOTULINUM*. K. F. MEYER and J. B. GUNNISON, J. Infect. Dis. **45:96**, 1929.

A comparative study of six purified strains of organisms isolated from several food specimens and one sample of soil obtained from Europe has revealed the following facts:

*Clostridium parobotulinum* type A strains indistinguishable from the American strains and the Lister strain 95 have been isolated from botulinogenous food products and a soil specimen. A type B strain of *Cl. parobotulinum* has been obtained from Italian commercially canned shallots.

A nonovolytic type B strain of *Cl. botulinum* recovered from a ham in Germany resembles morphologically, culturally and biochemically the original Elzezelles strain described by Van Ermengem and the various other strains studied by Schumacher, Ornstein, Bitter, Semerau and Noack, Bourmer and Doetsch and others. It differs from the Lister strain 94 by its inability to utilize inositol, its lower peptolytic properties, the production of a relatively weak toxin and the serologic ultraspecificity. The thermal death time of the spores of this organism is less than five minutes at 80 C.

AUTHORS' SUMMARY.



SOUTH AFRICAN CULTURES OF *CL. BOTULINUM* AND *PARABOTULINUM*. K. F. MEYER and J. B. GUNNISON, J. Infect. Dis. **45**:106, 1929.

A comparative study of eight cultures of anaerobes secured from South Africa has established the following facts. A nonovolytic, nonsarcolytic organism which elaborates a highly potent neurotoxin was found in two cultures. Pharmacologically, this poison acts like the botulinum toxin on small laboratory animals and monkeys. It is not neutralized by any of the known type A, B and C antitoxins. For this bacillus the designation *Clostridium botulinum* type D (Theiler and Robinson) is proposed. Two cultures although nontoxic contained anaerobic bacteria which corresponded morphologically, culturally and biochemically with the descriptions given by Theiler and Robinson for their *Cl. parobotulinum equi*. One culture when received contained a type A toxin. From this culture a moderately proteolytic *Cl. parobotulinum* type A which differs from the American and European strains of this species has been isolated. From a second culture an anaerobe with similar properties was demonstrated. The significance of these observations is discussed.

AUTHORS' SUMMARY.

CULTURAL STUDY OF AN INTERNATIONAL COLLECTION OF *CL. BOTULINUM* AND *PARABOTULINUM*. J. B. GUNNISON and K. F. MEYER, J. Infect. Dis. **45**:119, 1929.

Cultural, biochemical and serologic studies conducted with the simplest medium and by the use of the simplest technic with fifty-three strains concerned in human and animal botulism have shown that the action on native protein, the peptolytic property, the fermentation reactions, the agglutination and the toxin-antitoxin neutralization test are of importance for classification.

On the basis of cultural and peptolytic behavior the anaerobes are arranged in two groups: *Clostridium botulinum* (nonovolytic, Sørensen figures 1 to 6) and *Cl. parobotulinum* (ovolytic, Sørensen figures 18 to 21).

The agglutination tests subdivide the four, possibly five, toxicologic types (A, B, Ca, C $\beta$  and D) into at least fifteen subgroups while the fermentation reactions place the strains in at least eight groups.

Strains fundamentally different from those commonly encountered on the North American continent have been isolated in Europe, Australia and Africa.

AUTHORS' SUMMARY.

BOTULISM DUE TO HOME CANNED BARTLETT PEARS. K. F. MEYER and J. B. GUNNISON, J. Infect. Dis. **45**:135, 1929.

A mother and a daughter tasted and swallowed portions of sliced home preserved Bartlett pears which had shown definite signs of spoilage and fermentation. Symptoms of botulism developed within from five to six hours and death occurred within thirty and forty-two hours respectively after the fatal meal.

The pears were probably preserved by the open kettle method. They contained *Cl. parobotulinum* type A toxin (guinea-pig MLD, 0.001 cc.). The reaction of the syrup was  $p_H$  3.86. Aside from the toxicogenic anaerobe, a yeast and a representative of the lactobacillus group were isolated in pure culture.

Experimental studies have shown that *Cl. parobotulinum* found in the spoiled pears produces spores which survive from two to three hours boiling. They may germinate and elaborate the deadly poison in cooked Bartlett pears irrespective of the acidity, provided certain bacteria or yeasts are growing concomitantly.

Heated spores of *Cl. parobotulinum* failed to germinate in tubes of sterile pear juice with the  $p_H$  adjusted to 6. Although in several instances heated spores germinated and multiplied when inoculated into jars or cans of pears, no toxin was produced.

It is probable that certain fruits and acid vegetables owe their immunity from botulinum spoilage less to their acidity than to the absence of food substances essential to the elaboration of toxin.

AUTHORS' SUMMARY.

THE OCCURRENCE OF *BACILLUS SORDELLII* IN ICTEROHEMOGLOBINURIA OF CATTLE IN NEVADA. IVAN C. HALL, J. Infect. Dis. **45**:156, 1929.

Two strains of a previously unidentified pathogenic anaerobe isolated in 1919 and 1921 by L. R. Vawter of Reno, Nev., from typical cases of icterohemoglobinuria in cattle and against which he prepared an effective antitoxic serum, have been proved to belong to the species *B. sordellii*. This is the third locality in the world in which *B. sordellii* has been recognized, previous cultures having been isolated in the Argentine and New York.

The Nevada strains of *B. sordellii* are regarded as probably secondary invaders in icterohemoglobinuria, the primary cause of which is believed to be *Bacillus hemolyticus*.

*Bacillus hemolyticus* resembles *B. sordellii* in its vegetative morphology and gram-staining reaction, its sluggish motility, its fermentation reactions with the exception of maltose and its action on gelatin, and differs from *B. sordellii* in its sparse production of spores by old cultures, its weaker proteolytic action, its failure to ferment maltose, its hemolytic action on blood in culture medium, its marked tendency to produce congestion in animals and in the specific antigenicity of its soluble toxin.

AUTHOR'S SUMMARY.

A METHOD FOR THE STUDY OF BACTERIOPHAGE MULTIPLICATION IN BROTH. F. M. BURNET, Brit. J. Exper. Path. **10**:109, 1929.

A method is described by which the first stages of multiplication of a single phage particle in broth can be followed. The results show that the first increase occurs suddenly. In the two cases described there is a sudden appearance of about ten and of about forty demonstrable particles where one was present initially. The time of first increase after addition of phage may vary widely for different types of phages and for different particles in the same filtrate. Phage increase in broth is due, in the early stages at least, to the liberation at lysis of particles that have multiplied in or on a sensitive bacterium.

AUTHOR'S SUMMARY.

INOCULATION OF TYPHUS FEVER BY THE NASAL AND CONJUNCTIVAL MUCOSAE. HELEN SPARROW and UGO LUMBROSO, Arch. Inst. Pasteur de Tunis **18**:1, 1929.

Charles Nicolle established the fact that typhus fever is transmitted by lice through the act of feeding. Subsequently it was found that the intestinal content of the louse is infectious when applied to the bruised or cut skin. It was moreover noted that an accidental contamination of the conjunctiva with virulent material caused the disease.

The experiments reported by the authors were the inoculations of guinea-pigs by way of the healthy conjunctiva. The virus used was a laboratory strain transmitted from animal to animal by inoculation of cerebral tissue from infected guinea-pigs. The results obtained are to the effect that it is possible at times to infect guinea-pigs by placing the typhus virus on the healthy conjunctiva. Positive results are still more often obtained when the conjunctiva is previously prepared with bile. In animals infected in this manner, the incubation period is long, and the disease is mild and not followed by the development of an immunity. Guinea-pigs infected by way of the nasal mucosa invariably contract the disease. Sparrow and Lumbroso believe that the difference in the results obtained is caused by the fact that the eye represents a small surface absorbing an insignificant amount of material, which is not the case with the mucous membrane of the nose.

B. M. FRIED.

PATHOGENIC POWERS OF *B. MELITENSIS* AND *B. ABORTUS* FOR MAN AND FOR MONKEY. E. BURNET and E. CONSEIL, Arch. Inst. Pasteur de Tunis **18**:21, 1929.

Five years ago the authors concluded from experiments on man and on monkeys that *Bacillus abortus* was differentiated from *B. melitensis* by lack of pathogenic

power. Also, it was concluded that *B. abortus* vaccinates man and monkey against *B. melitensis*. The matter has been reinvestigated because of many reports of undulant fever in which there is an association with cows and in which *B. melitensis* is not suspected. The cultures used in the present work were more recently isolated than those used in the old experiments. The results secured on three monkeys and three men were similar. *B. abortus* vaccinates against *B. melitensis* but does not give true undulant fever. There was, however, some reaction. Fifteen days after inoculation two monkeys gave positive blood cultures. The serum gave positive agglutinations in dilutions from 1:200 to 1:500. The three men became allergic as determined by an intradermal test. All gave positive agglutinations. The immunologic results differed from the 1922 results, at which time essentially no immunologic reactions were observed. One monkey inoculated with a strain of "human abortus" gave an abortus reaction on a cynomolgus monkey. Thus the conclusions are less categorical than those in 1923. Vagaries indicate the necessity for further study and suggest the possibility of the adaptations of strains to new environment. Laboratory and epidemiologic correlation must be insisted on.

M. S. MARSHALL.

CHRONIC KALA AZAR IN TUNIS. CHARLES NICOLLE and CHARLES ANDERSON, Arch. Inst. Pasteur de Tunis **18**:63, 1929.

Twelve case reports of kala-azar in Tunis are added to reports of seventy-three previously published cases.

M. S. MARSHALL.

EXANTHEMATOUS FEVER, ITS IDENTITY WITH INFECTIOUS ERYTHEMA OR EXANTHEMATOUS FEVER OF THE MARSEILLES REGION AND THE "FEBBRE ERRUTIVA" IN ITALY. E. CONSEIL, Arch. Inst. Pasteur de Tunis **18**:86, 1929.

In a general article the author gives the history, clinical study, case reports, laboratory researches, etiologic table of observations for from 1902 to 1929 and the differential diagnosis. His final paragraph follows:

"Eruptive fever is clinically and etiologically differentiated. This has been felt and described by all authors who have observed cases of eruptive fever. They have described without hesitation a new disease, which they have observed under different names, in identical fashion. Comparison of patients of several regions show to the observer that the eruptive fever, infectious erythema and "febbre errutiva," is a single specific disease for which should be given the first name under which it was described, that of "fièvre boutonneuse."

M. S. MARSHALL.

ANGINA LEPTOTHRICA. A. JOSEPH, Deutsche med. Wchnschr. **55**:656, 1929.

The organism causing a chronic pharyngitis characterized by stippled, firmly adherent, yellow deposits in the mucosa without systemic disturbance was found in two patients to be *Leptothrix buccalis*.

PAUL J. BRESLICH.

SPIROCHAETA PALLIDA IN THE TISSUES OF INFECTED MICE. F. JAHNEL and R. PRIGGE, Deutsche med. Wchnschr. **55**:694, 1929.

In seven white mice inoculated intraperitoneally with material from primary syphilitic lesions, spirochetes were demonstrated in the lymph nodes of the groin and axilla, and in the popliteal lymph node in one mouse. The infection was symptomless, but in sections of the tissues, spirochetes were found, especially in the kidney but never in the central nervous system. The mice were killed at intervals of from sixty-seven to one hundred and seventy-nine days after inoculation.

PAUL J. BRESLICH.

## Immunology

THE SENSITIZATION OF RABBITS TO PRODUCTS OF THE PNEUMOCOCCUS. C. G. BULL and C. M. MCKEE, *Am. J. Hyg.* 9:666, 1929.

Rabbits having recovered from an acute infection with pneumococci are hypersensitive to an autolysate of the homologous organism. The hypersensitive state can be demonstrated from forty-eight hours to at least four months after the infection, the height occurring shortly after recovery from infection. Immunized rabbits are also sensitive to the autolysate, but to a less degree. Rabbits having recovered from infection with pneumococci and having been made carriers of *Bacterium lepi-septicum* developed infections by the latter organism within a few hours after pneumococcus autolysate was put into the nostrils, probably because of hypersensitive shock of the tissues of the portal of entry. PEARL ZEEK.

AN ENQUIRY CONCERNING THE RÔLE OF ALLERGY, IMMUNITY AND OTHER FACTORS OF IMPORTANCE IN THE PATHOGENESIS OF HUMAN TUBERCULOSIS. ARNOLD RICE RICH and HOWARD A. MCCORDOCK, *Bull. Johns Hopkins Hosp.* 44:273, 1929.

The authors present an analysis of the principal factors concerned in the pathogenesis of tuberculosis based on an extensive postmortem experience (200 autopsies on patients ranging in age from 7 weeks to 73 years) and experimental inoculations (1,000 animals) mainly into guinea-pigs and rabbits, carried on during the past several years. "Virulence" is regarded as merely the relative ability of the particular strain of tubercle bacillus under consideration to grow in normal individuals of an animal species that is naturally susceptible to the type from which the strain in question is derived. Resistance is not type specific and infected animals become only relatively immune. Issue is taken with Krause's view on allergy that following infection the body requires an altered reactivity or "altered attitude" toward the bacillus, and it is believed that this altered reactivity is essentially quantitative rather than qualitative. It is not an accurate generalization to say that the reaction to the first contact with the bacillus is always tubercle formation, and that exudative inflammation never occurs except in the allergic animal. Either the normal or the allergic animal can respond with either tubercle formation or exudative inflammation and the type of reaction will depend greatly on the number of bacilli and where they lodge. There is no proof that hypersensitiveness is responsible or necessary for the delayed spread, or for the more prominent death of the bacilli in the infected, resistant body. The mechanical effect of the allergic acute inflammation is not the fundamental mechanism which holds the bacilli of reinfection locally. Although it is at present widely believed that the allergic reaction is an essential mechanism of immunity, there is no proof that this reaction is necessary for the more rapid death of bacilli in the immune body. The essence of the matter of acquired resistance is that the bacilli cannot thrive as well in the previously infected body as in the normal one; although at present unable to speak with certainty of the meaning of allergy in relation to immunity, the authors believe that the bodily change responsible for this acquired interference with the life of the bacillus is, in whatever it consists, separate and distinct from the forces that are concerned in the allergic inflammatory—necrotizing tendency. Any beneficial effect that may follow treatment with tuberculin is less referable to perifocal inflammation than to desensitization, and the "stimulation of fibrosis" by perifocal allergic reactions is unnecessary. Encapsulation of a tuberculous focus by connective tissue is merely a process of nonspecific repair and is not a part of the process of inflammation. The allergic hypersensitive reaction is not specifically an attack on living bacilli but follows, in extreme degree, the injection of a simple water extract of the powdered bacillus. The allergic state in tuberculosis represents an increased capacity on the part of the tissues to react, not against living bacilli, but to a bacterial antigen that is liberated as a result of the disintegration of the bacilli, and the authors believe that the

mechanism leading to the death of the bacilli is in operation before the allergic reaction begins. The inflammation of allergy is protective only in that it helps neutralize the injurious effects of the products of bacterial disintegration in the hypersensitive body. An animal may be highly anaphylactic to tuberculo-protein and yet possess not the slightest degree of acquired immunity, or it may be highly immune to the bacillus, after infection, and yet not at all anaphylactic to tuberculo-protein. Although tuberculo-protein calls forth the allergic inflammatory reaction it never causes the formation of tubercles. The allergic resistant body does not change the bacillus of infection so that when introduced into a normal animal it produces a lesion different in any way from that which it originally produced. Unquestionably, with the proper dose properly placed, either the allergic or the nonallergic body can be made to react with either exudative inflammation or tubercle formation, but the allergic body has a markedly greater tendency to react exudatively than has the nonallergic. Any absolute and dogmatic distinction between the types of lesions developing under these two states of reactivity is unwarranted. The terms "exudative" and "proliferative" are useful for the description of what is seen in any case, but are dangerous if used as catch words, or as synonyms for states of resistance.

Miliary tuberculosis must be regarded as nothing more than the result of a septicemia with the tubercle bacillus. So far as is known, there is no inherent difference between the normal bodies of children and of adults which might account for the observed differences in reaction to the bacillus. The essence of the resistance question seems to lie not in the ability of the body to form connective tissue about the bacilli but in the inability of the bacilli to propagate freely in the particular body in question. In place of Krause's aphorism that "the patient is as resistant as the shell of his tubercle" the authors believe that "the patient is as resistant as his acquired ability to hold in check the growth of tubercle bacilli." The lymphatic anatomy of the lung of human beings at different age periods is of little importance in determining the distribution or character of tuberculous involvement, or the degree to which the regional nodes will be involved. The division of tuberculous infection into three stages comparable to syphilis (according to Ranke) is artificial, unnecessary and unsupported by fact. To say from sections from a case of tuberculosis with certainty just what has happened to the individual is completely out of the question, for the decision is always the result of: (1) the number of bacilli originally deposited at the site, (2) their virulence, (3) the length of time they have been at that particular spot, (4) the character of the tissue in which the bacilli lodge, (5) the degree of resistance (natural, individual and acquired) of the person and (6) the degree of allergy. Even massive blood stream infection in the human being does not produce extensive areas of tuberculous pneumonia. Areas of fresh caseous pneumonia of any extent are not produced in the human being in any other way than by the discharge of bacilli or bacillary products directly into alveoli from older foci in communication with bronchi, for only in this way can large numbers of bacilli reach a large area suddenly. The authors have never failed to find a discharging focus of this sort in their autopsy material when large areas of tuberculous pneumonia were present. Disseminated small foci of pneumonia can result from infection of the lung by way of either the blood stream or the bronchi. The pulmonary lesions of adult life in civilized communities are almost invariably lesions of reinfection, whether exogenous or endogenous in origin, and they begin as a rule, for reasons which are not yet clear, at or near the apex of the lung. The various types of lesions and reactions in the lungs of adults and children are discussed in the light of the authors' conceptions, and these principles are applied to the pathogenesis of the diffuse exudative tuberculous meningitis. The factors of high allergy plus the presence of abundant circulating bacilli are not sufficient in themselves to bring about exudative tuberculous meningitis in rabbits and guinea-pigs, but the direct injection of tubercle bacilli into the subarachnoid space is successful. A careful search for local caseous lesions in communication with the meninges serving as a foci of discharge of bacilli directly into the subarachnoid

space was successful in thirty-eight or forty cases of diffuse tuberculous meningitis; in seven, no generalized miliary tuberculosis existed, but one or more caseous foci existed in the brain. It is clear that disseminated tubercles in the brain are frequent complications of progressive visceral tuberculosis. Infection of the ependyma is not to be regarded as an evidence of blood stream dissemination of bacilli since bacilli can reach the ventricles by retrograde transport from the sub-arachnoid space. Tuberculous meningitis is not a direct result of local lesions which discharge bacilli into the subarachnoid space. Blood stream infection can occur as a result of tuberculous meningitis. What is true of the meninges is equally true of serous cavities in general; without question, in each such case a local tuberculous focus must have ruptured into the serous cavity—a caseous subpleural lymph node, a focus at the surface of the lung or a cold abscess in association with vertebral tuberculosis, discharging bacilli into a pleural cavity; a caseous focus in bone or cartilage discharging into a joint; a tuberculous Fallopian tube or caseous mesenteric lymph node discharging into the peritoneal cavity; a tuberculous lymph node involving the pericardium, or a direct extension from pleural tuberculosis.

H. J. CORPER.

STUDIES IN ISOHEMAGGLUTINATION: THEORETICAL CONSIDERATIONS.  
ALEXANDER S. WIENER, MAX LEDERER and S. H. POLAYES, *J. Immunol.*  
**16**:469, 1929.

Of all the theories on the heredity of blood groups that have been presented up to the present time, Bernstein's theory is most satisfactory. Apparent exceptions to this theory are due to: faulty technic; failure to test a sufficient number of people; errors in computation; failure to study a homogeneous group, and selection of a subgroup for study which is not representative of the entire group.

AUTHORS' SUMMARY.

QUANTITATIVE STUDIES ON THE ACTION OF COMPOUND HEMOLYSINS. RUDOLF GAHL, *J. Immunol.* **16**:483, 1929.

A quantitative study of the characteristic curves defined in preceding papers led to the conclusion that the complexities of these curves as they are experimentally obtained can be removed and the curves so simplified that they assume forms which are in harmony with the views proposed by Svante Arrhenius on the reaction between hemolytic amboceptor and complement by introducing the assumption into the calculation that neither heat inactivated hemolytic amboceptor serum is free from complement nor complement serum from natural amboceptor. Geometrical methods for introducing suitable corrections were developed for this purpose. The application of such methods permits the quantitative estimation of the contaminations. Heat inactivated hemolytic amboceptor serum may, when undiluted, contain complement in quantities not much lower in order of magnitude than the complement serum. Its effect may nevertheless not be noticeable on the Wassermann reaction as long as potent amboceptor serum is used which permits a correspondingly high dilution. Application of the law of chemical mass action makes the construction of theoretical systems of characteristic curves possible. Only the exponents of the mass law equations determine the shape of these curves. Such curve systems were calculated under various assumptions regarding the chemical combination between amboceptor and complement and found to present typical pictures characteristic of each reaction. It was shown that when the corrections referred to are applied to the curves derived from the law of chemical mass action in the opposite direction complex curves result which agree with those experimentally obtained within the limits of experimental errors except in the region of complement strength of amboceptor and complement were proposed. Rational systems for expressing regarding the relative molar concentrations of amboceptor and complement. The assumption of a stoichiometric chemical reaction between amboceptor and comple-

ment explains all observations. The stipulation of an enzymatic nature of one or both does not seem justified. Summing up the results of all four papers on this subject, we might state that while Manwaring rightfully pointed out that Arrhenius' mathematical representation of the reaction between hemolytic amboceptor, complement and red blood cells is not in agreement with the experimental facts, we find it in agreement with them so far as only the reaction between amboceptor and complement is concerned. The constants which Arrhenius used in his equations are as all constants obtained by experiment subject to revision by later investigators.

AUTHOR'S SUMMARY.

THE SKIN REACTION IN THE SENSITIZED GUINEA-PIG. SUSAN GRIFFITH RAMSDELL, *J. Immunol.* **16**:509, 1929.

Guinea-pigs actively sensitized and skin tested, using trypan blue as a technical aid, gave reactions to the antigen serum in dilutions as high as 1:10,000. Passive sensitization of the skin of a normal animal could be demonstrated as early as the sixth day after treatment of the actively sensitized animal, and was regularly more consistent than the test for passive sensitization by shock. Whether the antibody responsible for the skin reaction is a separate one from the anaphylactic antibody or merely an extension of its manifestation is not clear.

AUTHOR'S SUMMARY.

DISTRIBUTION OF ANTIBODIES IN THE SERUM AND ORGANS OF RABBITS. JULES FREUND, *J. Immunol.* **16**:515, 1929.

When rabbit serum containing precipitin is injected into the dermis of a rabbit, the site of injection reacts to a subsequent injection of egg white with specific inflammation (Arthus phenomenon). The state of sensitiveness is of short duration; it cannot be demonstrated from four to eighteen hours after passive sensitization. When rabbit serum containing agglutinins is injected into the skin of a rabbit, the agglutinins disappear from the skin within from six to twelve days. For the first five days the site of injection contains more agglutinins per gram of tissue than the noninjected parts of the dermis. Later the agglutinins are distributed in the blood and organs as if they had been injected directly into the blood stream. Precipitins and agglutinins differ from atopic reagins in regard to their fixation in the skin.

AUTHOR'S SUMMARY.

THE SCHICK TEST IN PALESTINE, A COUNTRY OF LOW DIPHTHERIA PREVALENCE. A. MANN and I. J. KLIGLER, *J. Prev. Med.* **3**:309, 1929.

Diphtheria and scarlet fever are relatively far less prevalent in Palestine than in countries having a temperate climate. From about 3,000 Schick tests it appears that the percentage of diphtheria immunes at the ages above 8 in Palestine is the same as found by Zingher in New York City, but that the immunization starts earlier among the Palestine children than in the New York children. A comparison of the native and foreign born groups on the one hand, and the Ashkenazic and Sephardic communities on the other, indicates that the native born, especially in the Sephardic community, develop their diphtheria immunity much earlier than the foreign born children. It would seem, therefore, that the absence of diphtheria in Palestine is only apparent. Since active immunity can probably be acquired only as the result of infection, the infection rate in the early age groups must be relatively high to produce so large a number of immunes.

AUTHORS' SUMMARY.

ANAPHYLACTIC STUDIES WITH EXTRACTS OF HYDATID SCOLICES. C. H. KELLAWAY, *Brit. J. Exper. Path.* **10**:115, 1929.

Experiments are described which attempt to correlate the characteristics of the hydatid scolex with those of other helminths, the tapeworm (Meyer) and the

flake (Kellaway). The substances in scolex which are insoluble in acetone but soluble in absolute alcohol and which act as "partial antigens," causing sensitiveness but being unable to discharge it, may possibly owe their activity in vivo to union with some body protein in the guinea-pig producing a foreign complex to which antibody can be produced. There is, however, in addition a water-soluble substance present in saline extracts of scolices which can function as an anaphylactic antigen. Owing to the difficulty of freeing scolices from the protein substances in hydatid fluid, it is not certain that this substance is not derived from hydatid fluid. Finally, host (sheep) serum protein is present in extracts of scolices, and extraction with pure dry acetone and with absolute alcohol does not guarantee its absence from the resulting extracts.

AUTHOR'S SUMMARY.

THE INFLUENCE OF PARENTERALLY GIVEN LIPOIDS ON HEMOLYSIN FORMATION IN RABBITS. HANS GROSS, *Centralbl. f. Bakteriologie*. **109:8**, 1928.

The simultaneous parenteral administration of cholesterol, lecithin and beef heart extract had no influence on the formation of hemolysin subsequent to the injection of sheep's red corpuscles.

PAUL R. CANNON.

THE RELATIONSHIP BETWEEN THE PHAGOCYTOSIS OF ANTIGENIC SUBSTANCES AND ACQUIRED IMMUNITY. S. FUJITSUND, *Centralbl. f. Bakteriologie*. **109:93**, 1928.

The author attempted to correlate the degree of phagocytosis of killed staphylococci following the previous injection of heated and unheated centrifugates of a cholera vibrio vaccine as well as salt solution alone, with the resulting antibody content of the blood. His conclusions are that the antibody content varied directly with the previous phagocytic rate in the same animal.

PAUL R. CANNON.

ENDOCRINE GLANDS AND IMMUNITY. A. SEITZ, *Centralbl. f. Bakteriologie*. **109:115**, 1928.

The phagocytosis of anthrax bacilli in vivo was markedly reduced in the serum of adrenalectomized rats. Simultaneous castration had no further effect. There was also a decrease in the content of bacteriolytic antibodies for the same bacilli. Coincidentally, there was a leukopenia of the neutrophils with a lymphocytosis and a thrombopenia. The injection of adrenal extract had no influence on the course of the infection.

PAUL R. CANNON.

THE SIGNIFICANCE OF THE SPLEEN IN SPIROCHETAL INFECTIONS. P. REGEN-DANZ, *Centralbl. f. Bakteriologie*. **109:321**, 1928.

Regendanz studied the course of infection in opossums artificially infected with *Spirochaeta didelphys*, especially as to the influence of splenectomy. Only two of nine normal opossums died as a result of the infection, whereas all eight of the splenectomized animals died, within a shorter period than the two normal ones. In opossums with a latent infection, splenectomy was followed by a rapid reproduction of the spirochetes. The author concludes that in this spirochetal infection the spleen plays the most important rôle in the formation of antibodies and the establishment of immunity.

PAUL R. CANNON.

A NEW METHOD FOR THE PRODUCTION OF A POTENT DIAGNOSTIC SERUM AGAINST ANTHRAX BACILLI. RAHEL ROSENBERG and D. ROMANOW, *Centralbl. f. Bakteriologie*. **110:102**, 1929.

The reliable diagnosis of anthrax demands a serum of high titer and specificity. The authors obtained this by the immunization of rabbits with the albumin extract of anthrax bacilli, prepared by the method of Fudjiwara (*Ztschr. f. d. ges. gerichtl. Med.*, 1922, Bd. 1), slightly modified. Serums highly specific and with titers as



high as 1:100,000 were thus obtained. Organ extracts from animals infected with anthrax gave precipitation reactions with these serums. The serums also retained their strength for long periods, but were of no value therapeutically.

PAUL R. CANNON.

THE RÔLE OF THE SKIN IN THE PRODUCTION OF SPECIFIC ANTI-ANTHRAX SERUMS. G. KUDRJAWZEW and D. ROMANOW, *Centralbl. f. Bacteriol.* **110**:164, 1929.

The intracutaneous injection of a virulent culture of anthrax bacilli into horses over a period of three months led to no formation of specific antibodies that could be detected in the blood. The later intravenous and subcutaneous injection of anthrax organisms into such animals was followed by a more rapid formation of antibodies than in animals not previously injected intracutaneously.

PAUL R. CANNON.

TUBERCULIN ALLERGY AND IMMUNITY IN TUBERCULOSIS. A. CALMETTE, *Ztschr. f. Tuberk.* **53**:193, 1929.

The traditional opinion that immunity is impossible without allergy is erroneous. It has been shown in various experiments that animals infected with a small amount of tubercle bacilli may lose their allergy after a time and still show a definite resistance against reinfection, and that animals may harbor tubercle bacilli or even healing tuberculous lesions without being allergic. The immunity is dependent only on the presence of living tubercle bacilli regardless of the absence or presence of allergy. This concept is borne out by the experiments with B. C. G. immunization in babies, who frequently do not develop allergy and still are undoubtedly protected from reinfection. Following oral immunization, at least 50 per cent of children develop allergy at some time or other within the first year; following subcutaneous immunization, all children develop allergy.

MAX PINNER.

## Tumors

LEUKOSARCOMA. DAVID H. FLASHMAN and SIMON S. LEOPOLD, *Am. J. M. Sc.* **177**:651, 1929.

A white man, aged 60, had a swelling in the right groin for a year. Biopsy revealed lymphosarcoma. The leukocyte count was normal. He was given treatments with roentgen ray for about five months, during which the blood was still normal. A month later, he developed leukemia, and the count rose to 444,000 cells per cubic millimeter with from 90 to 96 per cent small lymphocytes. At autopsy, the changes were of a character intermediate between lymphosarcoma and lymphatic leukemia, rather than a combination of changes marking two separate entities.

PEARL ZEEK.

TUMORS AND TUMOR-LIKE LESIONS OF THE BREAST IN ASSOCIATION WITH PREGNANCY AND LACTATION. A. R. KILGORE, *Arch. Surg.* **18**:2079, 1929.

Appended to this article is a discussion by Dr. Bloodgood on the treatment of "lactation tumors" and their diagnosis. Dr. Bloodgood strongly favors the use of frozen sections. Dr. Kilgore analyzed these tumors in an effort to determine their etiology and course. In a review of the literature, it was found that of 1,521 lesions of the breast, not including chronic cystic mastitis and acute inflammatory mastitis, 6.3 per cent were first observed by the patient in connection with pregnancy or lactation. Of these lesions, 83 per cent were cancers, galactoceles, tuberculosis or encapsulated adenomas. Twenty-six per cent of the cases of tuberculosis of the breast were first discovered during pregnancy or lactation. Possibly, this might be attributed to the increased functional activities, causing lighting up of a latent focus. More than 90 per cent of the cancers were in women above the age

of 30, and nearly 70 per cent of the benign tumors were in women under 30. It was found that all varieties of tumor may be observed by the patient at any stage in pregnancy or lactation. Of forty-six lactation cancers, eight were well after from four and a half to twenty-one years. Of seven cases without involvement of the axillary glands, five were cured, and of 26 cases with involvement of the axillary glands, three were cured.\*

N. ENZER.

RADIO-SENSITIVE INTRA-ORAL TUMORS. MAX CUTLER, Arch. Surg. 18:2303, 1929.

In the past few years, a group of tumors that occur in the nasopharyngeal and tonsillar region has been recognized from two points of view, namely, their histologic structure and their reaction to radiation. There are two main types: those in which there is an epithelial and lymphoid structure, conveniently called lympho-epitheliomas; and epithelial and transitional cell tumors exhibiting the anaplasia of epidermoid carcinoma. In the former there are syncytial masses of cells like epithelial cells, and the tumor is diffusely infiltrated with lymphocytes. In the latter there is a diffuse epithelial structure and absence of lymphocytes. Lympho-epitheliomas have been described as occurring in the tonsillar region and in the pharynx. Their structure resembles that of endothelioma or reticulum cell lymphosarcoma. The dual histologic picture forms the basis of the term "lympho-epithelioma." These tumors are relatively rare, only 6.3 per cent having been found in 300 tumors of the tongue, tonsils and nasopharynx in Ewing's experience. The transitional cell carcinoma is an undifferentiated, neoplastic, large cell tumor somewhat resembling large cell lymphosarcoma. Early involvement of the regional lymph nodes occurs here. This group comprises about 10 per cent of the epitheliomas of the nasopharynx. The primary lesion of these tumors is small, frequently insignificant and difficult to discover. The tumors often become manifest at first by cervical adenopathy. Visceral metastases are common. The liver and retroperitoneal lymph nodes, bones and vertebrae have been the seats of the metastases of this tumor. Clinically, patients usually present themselves on account of cervical adenopathy, and ulceration and pain and bleeding in the primary tumor may not occur until late. This group of tumors is particularly sensitive to radiation. Rapid regression and disappearance of both the primary lesion and the adenopathy occur in response to relatively weak doses. The tumor recurs rapidly, unless the radiation is continued to the point of sterilization. Nine patients who had this disease are reported to be well and apparently free of it after three years.

N. ENZER.

SKIN PRINTS IN LESIONS OF THE BREAST. J. O. BOWER and J. H. CLARK, Arch. Surg. 18:2386, 1929.

The authors present several prints of the breast showing the differences in the pores and markings of the skin as between persons and as between lesions of the breast. It is claimed that this method demonstrates clearly differences in the skin not so well demonstrated by other methods. In malignant lesions, there is a tendency toward contraction of the pores of the skin if the tumor is more fibrous, whereas if the tumor is increasing rapidly, there seems to be a marked increase in the size of the pores. Thus far, no definite deductions have been made, yet it would seem that this method might uncover characteristic changes in the epidermis associated with lesions in the breast.

N. ENZER.

TUMOR FORMATION FOLLOWING FREEZING WITH CARBON DIOXIDE SNOW. I. BERENBLUM, Brit. J. Exper. Path. 10:179, 1929.

Repeated mild freezing of the skin of mice with carbon dioxide snow over a long period may lead to the development of malignant tumors. Only a small percentage of mice respond in this manner, and the time necessary to produce such tumors is much longer than with the use of a carcinogenic tar. When the skin

of mice is subjected to repeated freezing and tarring, warts appear at the periphery of the area frozen in about the same period of time as with tar alone. No warts appear to develop in the frozen area itself. The warts produced in mice treated with carbon dioxide snow and tar do not grow as rapidly, nor become malignant as soon, as those produced by tar alone.

AUTHOR'S SUMMARY.

SKIN REGENERATION AND CANCER. R. J. LUDFORD, *Brit. J. Exper. Path.* **10**: 193, 1929.

Repeated scarification of an area of the skin of the mouse does not result in an aberration of the process of repair nor induce cancer. An area of the skin that has been the site of repeated injury and repair is not more susceptible to the carcinogenetic action of tar than the normal skin.

AUTHOR'S SUMMARY.

STUDIES ON THE BEHAVIOR OF THE RETICULO-ENDOTHELIAL SYSTEM IN IMPLANTED TUMORS. BRUNO BORGHI, *Tumori* **3**:289, 1929.

According to Borghi, a study of the reticulo-endothelial system by means of vital staining of animals inoculated with tumors demonstrates that the animals carrying recent tumors show a hypertrophy and hyperplasia of the reticulo-endothelial system. This is particularly noticeable when the tumors develop slowly. After full development of the tumors, the reticulo-endothelial system undergoes atrophy. The author concludes that besides possessing many other functions the reticulo-endothelial system participates in the defense against new growths.

W. OPHÜLS.

CONGENITAL ADENOMA OF LUNG AND HYDROPS UNIVERSALIS. P. ESCH, *Arch. f. Gynäk.* **133**:32, 1928.

A case of congenital adenoma of the lung in an infant with universal hydrops and hydammion is reported. The tumor is considered as a hamartoma. Five reports of similar cases were found in the literature. A common cause for both conditions could not be established.

W. C. HUEPER.

THE VAGINAL PAPILLARY SARCOMA OF THE CHILD. K. ADLER, *Arch. f. Gynäk.* **133**:100, 1928.

A papillary fibro-epithelial tumor mixed with immature muscle cells and located in the vagina of a 2 year old girl is described. A review of sixty previous reports of cases and a discussion of the symptomatology and pathology of these tumors are given. They recur after removal, but form metastases only in the regional lymph nodes. The prognosis is extremely bad; only one case in which cure occurred is on record.

W. C. HUEPER.

THE HISTOLOGIC DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX. W. SCHILLER, *Arch. f. Gynäk.* **133**:211, 1928.

Among 135 cervixes of uteri removed for reasons other than carcinoma, Schiller found 4, or 2.96 per cent, that showed beginning carcinoma. The uteri were from women in the climacteric or postclimacteric age. These cancers were not detected before operation, in spite of repeated previous clinical examinations. Periodical examination of women therefore does not represent a final solution of the problem of the early recognition of carcinoma of the uterine cervix. The early uterine carcinoma is histologically characterized by a sudden change of the normal stratified squamous epithelium into an atypical, polymorphous, anaplastic epithelium. It may possess plump, irregular papilli of varying size, which may perforate into glands. A thickening of the epithelium may be present, but it is never marked. The sharp line of demarcation between normal and pathologic epithelium is usually oblique, extending more into the basal layer than into the

superficial zone of the normal epithelium. This carcinomatous coat can be explained only as a transformation of normal epithelium of the basalis into malignant cells, as there is no evidence of any destructive growth of the malignant epithelium, such as the presence of detritus and leukocytes. Special pathologic metabolic products of the cancer cells spread by way of the intercellular bridges to the adjacent cells, effecting a malignant change of these cells. The predominance of this process in the cells of the basal layer is responsible for the oblique shape of the line of demarcation. Disposition toward tumor is only present in embryonic cells or cells with embryonic qualities (basal cells). Ulcers in the carcinomatous region are secondary changes and not the primary cause of the cancer. These cancers not only grow by transformation of normal cells of the basalis, but also by direct proliferation of the malignant cells. Early carcinomas do not show any infiltrative growth. The transformation of normal cells into malignant cells is a sudden and not a gradual process. Only lesions which invariably become malignant should be called precancerous. He includes in this group leukoplakia of the tongue and mouth, but states that in only from 60 to 75 per cent of the cases does it become malignant. He regards Bowen's dermatosis as definitely malignant. The histologic evidence of early malignancy consists in the following observations: The nuclei of the basal cells are smaller than normal, plump, oval or round and located at different levels in the cells. The cells do not form a regular, single layer, but are somewhat irregularly placed, some lower, some higher, producing the impression of stratification. The line of demarcation against the connective tissue is always sharp. The basement membrane is absent in the cancerous region and thickened in the parts of the normal epithelium adjacent to the malignant portions. The differentiation between basal cells and cells in the spinous cell layer is indistinct. There is not any or only an incomplete transitional cell layer. Cells in this layer resemble usually the atypical basal cells. They have a small amount of cytoplasm and are closely packed. The cell outlines are indistinct. The cells are irregularly arranged, and are irregular in size and shape and stainability of cytoplasm and nuclei. The number of nuclei is increased. Mitoses may be frequent and atypical. The superficial layers of the cancerous coat do not show the degenerative changes present in normal epithelium. In several cases, the coat consisted of polygonal, polymorphous, large, spinuous cells that stained deeper than the normal epithelium. They represent a more highly differentiated type of cancer cell.

W. C. HUEPER.

EXPLANTATIONS OF HUMAN TISSUES AND TUMORS. K. HEIM, Arch. f. Gynäk. **134**:250, 1928.

Explantations of fetal tissues (spleen, heart, brain, skin, ovary, endometrium) were successfully done. Amnion and chorionic villi could be constantly cultured. Chorionic villi did not grow after the fourth month of pregnancy. Growth of syncytial elements was never observed. Langhans' cells originate apparently from mesoblastic elements. They produced large masses of epithelioid cells in the cultures. Explantations of adult tissues were made from peritoneum and endometrium. Peritoneal elements could be successfully cultured only during an early part of pregnancy. Endometrium grew well, but only from the basal parts. The significance of this observation for the implantation theory of endometriosis is emphasized. Cultures of decidua were only successful up to the fourth month of pregnancy. Tissues of chocolate cysts, and carcinomas of corpus and cervix uteri and ovary were successfully explanted. The degree of differentiation obtained by the cells in the culture is evidently the result not only of a predetermined cellular quality but also of environmental conditions.

W. C. HUEPER.

PRODUCTION OF THE FLEXNER-JOBLING TUMOR BY FILTRATES. R. ERDMANN, Ztschr. f. Krebsforsch. **27**:69, 1928.

Using a stock of closely inbred rats of apparently high susceptibility to the Flexner-Jobling tumor, Erdmann produced similar tumors in twelve of thirty rats

inoculated, using for the inoculation cell-free filtrates of the tumor. Nine of these animals had been subjected to preliminary injections of India ink.

H. E. EGGERS.

IMMUNIZATION PROCESSES IN MALIGNANT TUMORS. C. LEWIN, *Ztschr. f. Krebsforsch.* **27**:138, 1928.

Lewin regards such immunity as has been obtained against malignant tumors as due to the production of nonspecific antibodies formed during the metabolic stimulation that follows nonspecific protein therapy. This immunity is associated with a heightening of the leukocyte content of the blood.

H. E. EGGERS.

ROUS SARCOMA OF FOWLS. E. FRAENKEL, *Ztschr. f. Krebsforsch.* **27**:150, 1928.

From his experiments, Fraenkel concludes that there can be no question that the Rous sarcoma may be produced by cell free material. He disagrees with Gye's conclusion that a second excitant is necessary, since the filtrable agent alone in sufficient quantity produces tumor. In all respects, this agent conducts itself as a ferment; it is associated with the euglobulin portion of the albuminous content of the filtrate. To meet all the requirements of the phenomena of the action of this agent, it would appear necessary to regard it as a transferable, reproducing ferment, similar to the bacteriophages.

H. E. EGGERS.

METASTASIS OF ADENOCARCINOMA TO THE CHOROID. A. ZAMENHOF and M. PLONSKIER, *Ztschr. f. Krebsforsch.* **27**:217, 1928.

The authors report a case of metastasis to the choroid of the eye of what clinically was almost certainly a primary carcinoma of the stomach. In addition, there were evident symptoms of cerebral metastasis.

H. E. EGGERS.

STUDIES OF CANCER-PRODUCING AGENTS. C. C. TWORT and H. R. ING, *Ztschr. f. Krebsforsch.* **27**:308, 1928.

A study of the cancer-producing action of various oils showed that while sperm oil was apparently innocuous, the petroleum oils were dangerous to a certain degree, while shale oils compared well with coal tar. Of the petroleum oils, the high-boiling fractions showed the greatest toxicity, while the shale oils showed a wider range in this respect, the most active fraction being that of low boiling point. The exciting agent could be concentrated by means of methyl sulphite or ethyl alcohol, while diminution of the action, in part, could be accomplished by treatment with sulphuric acid or oxidizing or reducing agents. The most active substance studied by them was a synthetic tar prepared from pine. With this, most of the toxic material distilled over at from 200 to 300 F., with a pressure of 3 mm., and could be extracted with ethyl alcohol.

H. E. EGGERS.

ETIOLOGY OF UTERINE CANCER. G. G. TER-GABRIELIAN, *Ztschr. f. Krebsforsch.* **27**:362, 1928.

A study of the cases of uterine cancer appearing at the Butyrki-Ambulatorium at Moskow during the last five years (194 cases) led the writer to the following conclusions: The cases present no support for the infection or heredity theories of tumor inception. The most essential factor is chronic irritation, traumatic, chemical or thermal. In the female, the uterus is the most frequently attacked organ; frequent factors here are the complications of birth and induced and incomplete abortions; multiple normal deliveries cannot be regarded as a factor. Aside from irritant factors, an individual predisposition must be recognized.

H. E. EGGERS.

EFFECT OF THE SPLEEN ON TUMOR GROWTH. B. E. BRUDA, *Ztschr. f. Krebsforsch.* **27**:380, 1928.

The writer found that when, in experiments *in vitro*, tumor tissue of mouse was cultivated in the plasma of splenectomized rats, there was an enhancement of growth. He concludes that in the normal animal protective substances against tumor growth may be of splenic origin.

H. E. EGGERS.

ORIGIN OF CARCINOMA OF THE LIVER AND PANCREAS IN ASSOCIATION WITH DISTOMATOSIS. M. G. RUDITZKY, *Ztschr. f. Krebsforsch.* **27**:402, 1928.

There is here reported a case of primary carcinoma of the liver or pancreas, in association with a severe infestation with *Opisthorchis felineus*. The writer regards the association as unquestionably one of effect and cause.

H. E. EGGERS.

CONTRIBUTION TO THE STATISTICS AND CLINICAL OBSERVATIONS OF PULMONARY TUMORS. E. SCHOENHERR, *Ztschr. f. Krebsforsch.* **27**:436, 1928.

In Chemnitz since the war there has been an undoubted increase of malignant tumors, especially of pulmonary cancer. The proportion of this to the total incidence of carcinomas is here the highest in Germany, a fact he ascribes to the great use of motorized vehicles, with resultant contamination of the air.

H. E. EGGERS.

METASTASIS OF A UTERINE CARCINOMA INTO A RENAL HYPERNEPHIOMA. A. WALTER, *Ztschr. f. Krebsforsch.* **27**:451, 1928.

In a woman dying of uterine carcinoma with metastases to the liver, there was also a renal tumor that grossly and microscopically appeared to be an undoubted tumor of the Grawitz type. In this tumor were found islands of carcinomatous growth identical with the uterine metastases in the liver.

H. E. EGGERS.

THE AGENT OF THE ROUS SARCOMA. E. FRAENKEL, *Ztschr. f. Krebsforsch.* **27**:467, 1928.

Attempts at the cultivation *in vitro* of the filtrable agent of the Rous sarcoma were unsuccessful, although the agent remained active after seven days' incubation at 37 C. in sterile bouillon. While reducing agents did not affect the activity of the filtrate, this was rapidly destroyed by the introduction of oxygen.

H. E. EGGERS.

FREQUENCY OF CARCINOMA IN EPILEPTIC PERSONS. VOLLAND, *Ztschr. f. Krebsforsch.* **28**:15, 1928.

In 575 deaths of epileptic patients who were more than 40 years of age, the writer found a cancer mortality rate of 3.1 per cent which is about one third of the usual incidence in persons of similar age. The lower rate in epileptic persons the writer ascribes to the altered humoral and metabolic variations in that disease exerting a restraining influence on the development of cancer.

H. E. EGGERS.

TUBERCULOUS INFECTION OF TESTICULAR CARCINOMA. F. KLINK, *Ztschr. f. Krebsforsch.* **28**:38, 1928.

The writer reports a case of associated tuberculosis and carcinoma of the testis, in which all evidence favors the view that the carcinoma became secondarily infected. This evidence is: the absence of epididymal tuberculosis; the absence of tuberculosis in the noncancerous portion of the testis; the almost complete absence of tuberculous necrosis, and the scarcity of bacilli as indicating recent infection. A similar case has been reported previously by Sakaguchi.

H. E. EGGERS.

A METHOD OF ISOLATING TUMORS WITHIN AND WITHOUT THE ORGANISM. A. A. KRONTOWSKI, *Ztschr. f. Krebsforsch.* **28**:60, 1928.

The writer describes a method of so isolating tumors within the host as to secure the tumor free from contact with adjoining surfaces. This he accomplishes by introducing the fragment for inoculation into a kidney or portion of a kidney, dissecting this free to its pedicle, and enclosing the whole in a sterile gutta percha sac through which the pedicle enters. In this way the tumor grows with a single vascular supply, facilitating the study especially of metabolic changes in such growths.

H. E. EGGERS.

PROSTATIC CARCINOMAS—THEIR FREQUENCY AND THEIR METASTASES. R. PÜRCKHAUER, *Ztschr. f. Krebsforsch.* **28**:68, 1928.

Metastases to bone were found in 54.5 per cent of the fifty-five cases of prostatic carcinoma on which this report is based. In the thirty-nine cases in which the prostatic carcinoma was evidenced by marked changes in that organ itself, the percentage was considerably higher, 71.8. As regards location of the metastases to bone, the vertebrae showed the most frequent involvement; twenty-seven cases.

In the great majority of the cases, the bone involvement was of osteoplastic type. Next in frequency of involvement came the femur and the pelvic bones. In these cases there was metastasis to internal organs in only twelve cases, and in only one case was there metastasis to an organ without metastasis to bone. Attention is called to the frequency with which the cancerous alteration of the prostate is so minor as to be overlooked, except in microscopic examination.

H. E. EGGERS.

### Medicolegal Pathology

ACUTE ARSENIC POISONING. THEODORE L. ALTHAUSEN and LEWIS GUNTHER, *J. A. M. A.* **92**:2002, 1929.

Hair is one of the main channels for the elimination of arsenic from the body. The delayed appearance of arsenic in the hair, its relatively high arsenic content and the length of time during which this poison can be detected there make hair one of the most valuable objects for analysis in cases of suspected arsenic poisoning. The administration of sodium thiosulphate in the case in which it was given was accompanied by an increase in the excretion of arsenic in the air, urine and feces and by marked clinical improvement.

AUTHORS' SUMMARY.

FRACTURED CLAVICLE, THROMBOSIS OF THE RIGHT SUBCLAVIAN ARTERY, CEREBRAL EMBOLISM. A. G. YATES and D. GUEST, *Lancet* **2**:225, 1928.

In an epileptic woman, aged 41, the right arm and hand for some months were painful and weak, and when first examined the hand was cold and bluish; there was no pulse in the arm or hand. As she was about to enter the hospital, cerebral embolism occurred, and at the postmortem examination a short clot was found in the right axillary artery and one 4 cm. long in the first and second parts of the subclavian, beginning 1 cm. distal to its bifurcation. The embolism was in the basilar artery and was explained by a part of the clot in the subclavian getting into the right vertebral artery. Near the thrombosed vessels in the neck, there was an old ununited fracture of the right clavicle.

E. R. LECOUNT.

DEATH AT BIRTH FROM HEMORRHAGE INTO THE THYROID GLAND. MUTEL and MORIN, *Ann. de méd. lég.* **8**:157, 1928.

A woman, aged 28, the mother of two children, with whose birth there was no difficulty, found her third child dead about twenty-four hours after birth. This child also was born in normal labor and apparently was well when born. Because

of anonymous accusations, a postmortem examination was made, and the only alteration found anywhere was a hemorrhage into the thyroid gland. The gland was twice the normal weight, the hemorrhage entirely within the capsule, and in the other structures of the neck there was no evidence of injury.

It is well known that spontaneous hemorrhages into the suprarenal glands may cause death in both infants and adults. About seven deaths from hemorrhage into the parathyroid glands in infants from 3 to 6 months old have been reported. Similar hemorrhages into the hypophysis with corresponding serious consequences apparently have not been observed. Goiterous swelling of the thyroid gland due to hyperemia caused by passage through the birth canal is well known, and usually yields quickly to hot packs and other local treatment. Hemorrhages such as this reported by Mutel and Morin causing death are extremely rare. It was difficult to find any thyroid tissue microscopically, because of its mechanical displacement and destruction by the apoplexy in the gland.

THROMBOPHLEBITIS OF THE UPPER EXTREMITY FROM STRAIN. L. LOUIS-CAEN, *Ann. de méd. lég.* 8:188, 1929.

Reports have been made of about thirty cases of edema of the hand and arm caused by venous obstruction which, in its turn, has followed some unusual effort, such as violent abduction and rotation of the arm occurring in a fall, or repeated unusual but less violent strains. The relation of the edema, which does not always prevent working, to insurance and compensation is important.

A good résumé of the more recent literature is given with the report of a case in a carpenter whose obstructed circulation was not traceable to any unusual exertion. If one is to conclude that the venous obstruction is due to violence, the edema or other evidence of obstruction should be evident not later than a few days after the injury, and the presence or absence of disease causing or contributing to the thrombosis should be carefully determined.

E. R. LECOUNT.

TRAUMATIC ASCITES. WITAS and PARRES, *Ann. de méd. lég.* 8:239, 1928.

Three days after being dragged by a runaway horse and receiving many blows on the abdomen and legs, a man noted that his legs were cyanotic and his abdomen swollen. A physician then found fluid in the abdomen and subcutaneous abdominal veins dilated to compensate for an obstructed portal circulation. Five tapplings of the abdomen yielded 60 liters (60,000 cc.) of ascitic fluid; death occurred ninety-six days after the accident.

At the postmortem examination, no cause for the ascites was found, but in the account of this examination, it is not apparent that the inferior vena cava, hepatic blood vessels, liver or intrahepatic branches of the portal vein were thoroughly examined.

E. R. LECOUNT.

POSTPONED DEATH FROM TRAUMATIC HEMORRHAGE INTO THE FOURTH VENTRICLE. RENOUX, *Ann. de méd. lég.* 8:255, 1928.

A young man was found dead in bed fourteen or fifteen hours after a football game, with the bed clothes stained from what must have been projectile vomiting. A watchman in the hotel heard only profound snoring. The only symptoms the young man complained of after the game were slight photophobia and dizziness when he stood erect after sitting. The fourth ventricle was found full of blood, which had extended from a hemorrhage in the occipital lobe near the right lateral ventricle. There was a scalp contusion, but no fracture; the only injury anywhere was that of the head.

E. R. LECOUNT.

INDUSTRIAL DISEASES FROM RADIOACTIVE SUBSTANCES. M. DE LAET, *Ann. de méd. lég.* 8:443, 1928.

After the inclusion of many personal observations with a review of the literature, the following conclusions are stated: Contact with radioactive substances or



with their radiations causes, independently of external lesions, leukopenia and erythropenia, lowered blood pressure, sterility and sometimes leukemia; the disturbances of nutrition are not as well known; these effects occur early and when once established are tenacious. Although there are some individual variations in susceptibility, no one escapes altogether when exposure is at all prolonged or repeated. When the leukocytes are reduced to 2,500 or 3,000 and the red cells to not less than 2,500,000 or 3,000,000, the prognosis is not necessarily grave. These disorders from radioactive substances constitute an occupational disease; in determining compensation, the question of sexual potency or of sterility is important. Prevention and protective measures are discussed rather than the matter of liability; laborers exposed to these dangers should be examined frequently.

E. R. LECOUNT.

OCCUPATIONAL DISEASES CAUSED BY HYDROCARBONS AND THEIR PRINCIPAL DERIVATIVES. M. DUVOIR, *Ann. de méd. lég.* 8:453, 1928.

About forty pages are devoted to enumerating the many harmful substances in this chemical group, some of them natural products, most of them obtained by technical processes of isolation or synthesis. And with their description, the author cites the occupations in which their harmful action is likely to be encountered; he also gives brief accounts of the diseases they cause. Among the latter, poisoning from benzene is well presented.

E. R. LECOUNT.

ORIGIN OF THROMBOSIS IN VEINS. H. WILDEGANS, *Arch. f. Klin. Chir.* 148:592, 1928.

More water, residual nitrogen and lactic acid were found in the blood of the saphenous veins, especially in association with varicosities, than in the cubital veins of eighteen patients, all but two of whom were 40 years old, or older. No significant differences were demonstrable in the amounts of calcium, fibrinogen or thrombin. It is suggested that instead of emphasis being put on disturbances of the circulation, infection or alterations of the walls of blood vessels to explain postoperative thrombosis and embolism, attention ought to be directed to the modifications in the physical and chemical constitution of the blood.

In discussing this work of Wildegans, Nieden called attention to the increase of postoperative thrombosis and embolism in the earlier decades of life, as well as their actual increase. Schönbauer mentioned the slowness of clotting of blood in the portal vein, which takes fourteen minutes, as compared with eight minutes for the clotting of blood from the lower extremities, and the need of fluids after operations. Von Seeman spoke of the excess of globulin and fibrinogen in the blood after operations, their origin from wound exudates and damaged tissues and the way these substances rob red blood corpuscles and platelets of their electric charge; thus promoting agglutination and sedimentation. He referred to the value of dextrose and Ringer's solution in correcting the instability of the plasma caused by increase in globulin and fibrinogen and to the relatively greater increase of these in the blood of patients with cancer.

E. R. LECOUNT.

ACCIDENT, MULTIPLE MYELOMAS AND INSURANCE. M. LAESECKE, *Arch. f. Klin. Chir.* 149:123, 1928.

Complete paralysis of both arms was present the day after a blow had been received on the back of the head and neck by one of several iron plates that a man aged 53 was carrying while at work. When he entered the hospital fourteen days later, only portions of the fourth cervical vertebra were found by roentgen examination. The trauma had aided destruction of a vertebra already diseased with one of many myelomas in the bones, either then present or developing subsequently. In the decision of the questions of compensation and insurance, it was decided that the accident had been a contributory cause.

E. R. LECOUNT.

INCREASE OF POSTOPERATIVE THROMBO-EMBOLISM AND ITS CAUSE. F. PROCHNOW, Arch. f. Klin. Chir. **151**:99, 1928.

With a brief summary of the other published statistics of the remarkable increase in deaths from pulmonary embolism after operations, Prochnow reports thirteen deaths that occurred in the surgical clinic of Bakay at Budapest, eleven of them during the last five of the years from 1915 to 1927, during which they all occurred. The operations numbered 18,517. He divides cases of pulmonary embolism as follows: those in which death was unexpected and without any preliminary symptoms; those in which chest pain, dyspnea, cough and bloody sputum were observed, with death occurring in a few minutes or a few hours, and those in which there were similar symptoms followed by recovery or death much later from abscesses of the lungs or pyemia. In other respects, this résumé is like many others resulting from the observation of the increasing frequency of these deaths.

E. R. LECOUNT.

LACERATIONS OF THE ABDOMINAL ORGANS BY BLUNT FORCE. B. NEUKIRCH, Arch. f. Klin. Chir. **153**:23, 1928.

The spleen alone was torn in two bodies; the left kidney and spleen, in one body; the liver, urinary bladder and one kidney, each in one body; the ascending colon dorsally where it lies against the back wall of the abdomen and is not covered by peritoneum, in one body; the descending colon in the pelvis at the junction with the rectum, in one body; the transverse horizontal part of the duodenum, in one body; the small bowel, in three bodies, location not stated, but in one of the three the tear was attributed to an open hernial pouch; and finally, tears of the mesentery, in two bodies.

The author emphasizes that the loops of small bowel are able to move away and escape damage from blunt force and are usually torn at places such as the duodenojejunal junction, where they are fixed to the wall of the abdomen. He admits that when distended, the bowel is sometimes torn on being crushed because the content is not readily compressed and is unable to move along, the adjacent parts of the channel being also filled. Only one of the fourteen persons was a woman; death occurred in eight of the cases.

E. R. LECOUNT.

FRACTURES OF THE EPIPHYSES OF THE DISKS OF THE BODIES OF VERTEBRAE. G. SCHMORL, Arch. f. Klin. Chir. **153**:35, 1928.

In addition to the three centers of ossification, one for the body and one for each lateral half, there are a number of secondary centers from which a vertebra develops. The latter appear much later than the first, and unlike epiphyses of long bones, they are without much influence on the normal growth of the remainder of the vertebra. In a former report (Ueber bisher nur wenig beachtete Eigentümlichkeiten ausgewachsener und kindlicher Wirbel, Arch. f. Klin. Chir. **150**:420, 1928), Schmorl stated that epiphyses for the upper and lower disks of the body which face the intervertebral cartilages appear at the thirteenth year. He now reports the appearance of some of them at the eighth year. He found them in the seventh cervical and first thoracic vertebrae in lower disks, in the second thoracic in the upper, in the third, fourth, sixth and seventh thoracic in both and in the tenth thoracic only in the lower. It will be seen from this that they do not all appear at the same time. These disks, which ultimately unite with the remainder of the body of the vertebra, develop from separate centers, two in front and two behind, and their appearance is also discontinuous. The various stages of their development is important in reckoning the age of a person, but also with reference to both disease and injury. Schmorl mentions having once met with tuberculosis in one of the disk epiphyses, and in this article he reports fractures of three

One was a fracture of the upper border of the body of the eleventh thoracic vertebra sustained in the World War when the man was 20 years old and found

thirteen years later after he had died from tuberculosis. Schmorl found it after the skeleton was macerated. The broken segment was ventral, included about one third of the entire rim, and was displaced so as to lie lower than the remainder of the rim. After fracturing, it had healed displaced. The man consequently had this part of the vertebra as an ununited epiphysis in his twentieth year. The second case concerned a woman who died at 22 and who four years previously was injured. The fractured epiphysis was in the third lumbar vertebra. It is difficult to find these separate centers of ossification for the disks by slicing the vertebra, but they are easily found by roentgen examination, which, although useful, is not so necessary in the demonstration of fractures in the prepared bones.

E. R. LECOUNT.

DELAYED DEATH FROM CYANIDE POISONING. W. ERNST, *Deutsche med. Wchnschr.* **54**:1373, 1928.

There are a few reports of death five, six or even thirty-six hours after poisoning with cyanides, and by some the prognosis is regarded as favorable when death fails to take place within one or two hours. This report by Ernst deals with death twelve days after the onset of symptoms which, at the time, were regarded as from poisoning. After the death, a report from the medicolegal institute was returned that the poisoning was from potassium cyanide. The patient was severely afflicted with epilepsy and presumably poisoned himself, although the source of the poison was not learned.

E. R. LECOUNT.

ICTERUS FROM LEAD. C. LEWIN, *Deutsche med. Wchnschr.* **54**:1450, 1928.

Poisoning with lead, according to Lewin, may cause a pale skin with slight yellow discoloration of the sclera and bilirubin of the blood demonstrable only by the indirect reaction of van den Bergh. In this group, only urobilin or urobilinogen are in the urine, no bilirubin. With more pronounced icterus, both reactions for bilirubinemia are obtained, and the stools may be pale. Still more pronounced are the cases of acute yellow atrophy due to lead. Two of this last variety with cases of both other forms are reported.

E. R. LECOUNT.

DEATHS FROM THERAPEUTIC PUNCTURES OF THE THORAX. T. FAHR, *Deutsche med. Wchnschr.* **54**:1550, 1928.

In attempts to tap the pericardial sac, three deaths occurred because the heart was pierced with the needle. In two of these cases, the heart was compressed by blood in the sac so that death occurred; in the third, the sac was so torn that the patient, a 6 year old girl, died from the bleeding into the left pleural cavity. In one of the first two, the blood stained fluid in the pericardial sac amounted to 1,000 cc., the bleeding from the wound made by the needle in the heart having been added to a huge transudate previously in the sac.

Three other deaths were accompanied by wounds of lung tissue. One was that of a woman who as a result of heart disease had hydrothorax. After death, 1.5 liters (1,500 cc.) of blood was found in the left pleural cavity from a wound of the lung made one-half hour before death, when one liter (1,000 cc.) of fluid was withdrawn. The other two deaths in association with wounded lungs are not explained as satisfactorily by Fahr, because there was neither hemothorax nor any huge hemorrhages into the lungs. The symptoms accompanying one death suggest embolism of air into the coronary arteries or into both sets of vessels (see Rukstinat, G. J., and LeCount, E. R.: Air in the Coronary Arteries, *J. A. M. A.* **91**:1776 [Dec. 8] 1928); the symptoms preceding the other are not related.

E. R. LECOUNT.

SEQUENCES OF PENETRATING BULLET WOUNDS OF THE THORAX. M. ERNST, *Deutsche Ztschr. f. Chir.* **206**:294, 1927.

Many interesting observations are reported in an account mainly devoted to the amounts of pensions to be given different former soldiers in the World War. The

patients came to the surgical clinic of Sauerbruch from all over Germany, and there it was decided whether the missiles or fragments of projectiles should be removed. In the case of twenty-four who came it was regarded as unwise to attempt operation, and two of these subsequently died. Operation was not undertaken for these two because there was too much tuberculosis present in the lungs. Of the remaining twenty-two, many recovered so as to return to their occupations.

A few refused operation; one of these died soon after from hemorrhage; in another the foreign body pulsed with the pulmonary artery. Eighty were operated on, and the foreign bodies removed. From the release of intrathoracic pressure after artificial pressure, two died; a third died from pneumonia, and one more from sepsis. Of thirty-eight whose operation was thoracotomy, twenty-three returned to work; of five others there was no information and the rest were partly healed. Ten of the thoracotomies were done for hemoptysis; sixteen for abscess of the lung. In many of the patients, symptoms did not appear until many years after they had been wounded. The first symptom was frequently hemoptysis following some unusual exertion. Abscess or gangrene or hemoptysis was the main symptom, but in some of the soldiers, the first symptoms did not develop until ten years after they had been injured.

E. R. LeCOUNT.

#### RELATION OF INFECTION TO POSTOPERATIVE THROMBOSIS AND EMBOLISM.

W. STÖHR and F. KAZDA, *Deutsche Ztschr. f. Chir.* **208**:105, 1928.

With postoperative thrombosis established, subsequent local or generalized infection leads more frequently to multiple infarcts from the thrombus than to progressive extension of the thrombosis. Only two of thirteen deaths (15.33 per cent) were from huge emboli when there was a generalized infection or local infection of the wound; the other eleven were deaths from pyemia with multiple metastatic abscesses and septic infarcts. On the other hand, with no infection demonstrable by routine methods in eight bodies, there were seven deaths (87.5 per cent) caused by large emboli obstructing the pulmonary artery. When infection develops subsequent to the formation of clots in veins at some distance away from the site of operation, infarcts from small emboli are rare, and death results in more than half of the patients thus affected from large emboli which block the main branch of the pulmonary artery or its chief divisions. With no infection and thrombosis developing after operations in veins at some distance, death from embolism is frequent. This sort of death from large dislodged clots producing pulmonary embolism is as frequent without as with infection after operations.

Postoperative infection plays little part in causing progressive thrombophlebitis and sudden death from pulmonary embolism, and apparently is unconcerned with the formation of clots in veins at a distance. This last form of thrombosis is probably related to the disturbances of the bowels, and stomach following infection of wounds; also to constitutional peculiarities and the severe changes in metabolism which result from major operations. These conclusions resulted from a study of the records of 24,032 postmortem examinations, 20,654 with 134 deaths from postoperative embolism and twenty-four cases of thrombosis distant from the wound and in none of these twenty-four was there embolism of any kind; in a second group of 714 postmortem examinations thirteen deaths from embolism and in examinations made at a third place, all in Vienna, thirteen deaths from postoperative embolism in 2,664 necropsies. Stöhr was unable to find confirmation in this study for the opinion Aschoff expressed at the meeting of the German Naturalists in 1911 in Karlsruhe that thrombosis in veins quite removed from the wound is especially frequent after operations when infection is present.

E. R. LeCOUNT.

#### ARTHRITIS FROM FOREIGN BODIES IN THE JOINTS. O. F. EHRENTHEIL, *Deutsche Ztschr. f. Chir.* **208**:409, 1928.

In reporting removal of a needle from a knee joint treated for some time as tuberculosis, emphasis is given to the two forms of arthritis from foreign bodies

when no infection occurs: intermittent hydrops with metallic objects or fragments, and a second form with wood (sharp splinters, thorns, etc.) with a marked resemblance to hyperplastic tuberculous synovitis.

E. R. LeCOUNT.

RELATION OF INJURY TO A SECONDARY THYROID GLAND CARCINOMA OF THE RIGHT FEMUR. E. BRINKMANN, *Klin. Wchnschr.* 6:1903, 1927.

Although no primary tumor was demonstrated, it was decided that the injury of the right femur had brought about the location there of thyroid tissue which produced an adenocarcinoma found by roentgen examination ten weeks after the fall, and subsequently verified microscopically. A piece was cut out for microscopic examination a week after the growth was demonstrated roentgenoscopically, and the tissue was again examined after amputation eighty-six days after the injury. The patient was a woman 45 years old. The thyroid gland was not altered in any way clinically demonstrable, nor any evidence obtained of other metastatic growths. Shortly before amputation, the femur broke where the growth was located.

E. R. LeCOUNT.

OCCUPATIONAL ACTINOMYCOSIS. RECKZEH, *Klin. Wchnschr.* 7:2299, 1928.

The possibility that actinomycosis can be incurred independently of the occupation, threshing of rye, resulted in the refusal of petitions of the widow for compensation. The actinomycosis was abdominal, and it was claimed that the fungus was swallowed with dust from the grain, which got on the food. On the other hand, it is of interest that the German regulations for compensation for accidents sustained in various occupations prescribe payment of claims for anklyostomiasis acquired by laborers employed in digging tunnels.

E. R. LeCOUNT.

EPILEPSY FOLLOWING BENZINE POISONING. G. STIEFLER, *Wien. med. Wchnschr.* 78:938, 1928.

Rendered unconscious by benzine vapors as he was busy in a tank for benzine, 13 feet deep, which was being emptied, a man, aged 35, suffered for many hours with asphyxia and tonic muscle spasma. He left the hospital after ten days, and typical epileptic attacks began three months later. They recurred every four to five months. He was not neuropathic and no history of epilepsy previous to the poisoning was obtained. It was assumed that changes in the brain from benzine had some causal relation to the development of the attacks.

E. R. LeCOUNT.

BISMUTH POISONING FROM BECK-PASTE. P. TORRIONE, *Schweiz. med. Wchnschr.* 58:895, 1928.

An empyemic fistula was packed with Beck paste repeatedly, so that altogether 1,500 Gm. was used. This contained 150 Gm. of bismuth. Healing took place in two months. One month later, when stomatitis with superficial ulcers appeared, the fistula was reopened and 60 Gm. of a dark fluid was removed. Torrione says that bismuth poisoning in this way is frequent, and that measures to prevent it are: injecting only a little at a time; not using it in cavities freshly curetted, and never allowing it to remain in the cavities for more than five days. Injection of the paste should always be done slowly.

E. R. LeCOUNT.

## Technical

COMMENTS ON THE IMPREGNATION OF NEUROGLIA WITH AMMONIACAL SILVER SALTS. NATHAN CHANDLER FOOT, *Am. J. Path.* 5:223, 1929.

The technic recommended by Kubie and Davidson, of the Rockefeller Institute, for preparing solutions of ammoniacal silver salts for the impregnation of brain tissue has been found, on trial, to give results commensurate with its chemically

correct basis and far superior to those obtained by using the more roughly prepared solutions now in general vogue. It is found that silver diaminohydroxide gives excellent results in the impregnation of astrocytes, while silver diaminocarbonate concentrates chiefly on the oligodendroglia and microglia. If mixtures of both salts are used, as is the case with most of the inaccurate methods now employed, the impregnation is of a more general nature, but inferior in its specificity to that obtained through the use of pure salts. If the 1 per cent neutral formaldehyde in general use for developing sections impregnated with either of these double salts be buffered with a little sodium carbonate, a definite improvement in the development of the sections follows; the impregnation is more uniform, is freer from incrustations and precipitates and shows more precise definition of the neuroglia. No one method is recommended, the reader being left to draw his own conclusions and choose for himself that technic which will suit his particular needs; it is considered that the subject is fully enough set forth to afford him an opportunity for devising his own procedure. The excellence of silver diaminohydroxide should, however, be stressed.

AUTHOR'S SUMMARY.

ISOLATION AND CULTIVATION OF THE MENINGOCOCCUS. RUTH GOSLING, J. A. M. A. 93:611, 1929.

Excellent results are reported by Gosling in the use of a dextrose semisolid medium for the cultivation of the meningococcus. The medium is prepared by adding 1 per cent of dextrose and 0.25 per cent of agar to nutrient veal infusion broth, adjusting the reaction to  $p_H$  of from 7.2 to 7.4, and sterilizing 10 cc. amounts in tubes in the Arnold sterilizer one hour on two successive days. A large loopful of sediment from spinal fluid that has been centrifugated at high speed from five to ten minutes is inoculated into the upper half inch of the medium and a deep stab made. Growth appears in from eighteen to ninety-six hours, and the meningococcus has remained alive as long as two and one-half months.

TITRIMETRIC MICRODETERMINATION OF PHOSPHORUS IN SERUM AND FLUIDS. K. SAMSON, Klin. Wchnschr. 8:1029, 1929.

With from 1 to 2 cc. of serum or fluid, the estimations are made by precipitating the phosphorus in a protein-free filtrate (trichloroacetic acid) as molybdate, dissolving the precipitate after washing it free of acid in N/40 NaOH, and removing the ammonia by the addition of formaldehyde. Retitration with N/40 HCl determines the amount of N/40 NaOH utilized. The volume (in cubic centimeters) of alkali utilized, multiplied by 0.0277, equals the milligrams of phosphorus in the sample. The original article should be consulted for further details. Accuracy is claimed to within about 1 or 2 per cent.

EDWIN F. HIRSCH.

# Society Transactions

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## THE PHILADELPHIA PATHOLOGICAL SOCIETY

*Regular Meeting, March 14, 1929*

HAROLD J. AUSTIN, *President*

MELANOTIC TUMOR IN *LOPHIUS PISCATORIUS* (ABSTRACT). HELEN INGLEBY.

A melanotic tumor is described as having occurred under the epithelium of *Lophius piscatorius*. It was a black warty growth which projected above the level of the skin. It consisted of large branched cells loaded with masses of pigment, which in most cases completely obscured the nuclei. These chromatophores were of the same type as those under the normal epithelium, but more irregular. The main mass of the tumor lay above the level of the skin, was unencapsulated and was sharply demarcated from the subcutaneous tissue. The tumor showed a tendency to spread laterally rather than downward; the lateral offshoots were more loosely arranged and hence not so clearly demarcated from the surrounding tissues. Connective tissue septums seemed to divide the tumor into lobules. Groups of small, rounded, compact pigmented cells surrounded by connective tissue sheaths were seen, but not explained. Blood spaces were seen in the central part of the growth, together with numerous blood vessels. Groups of inflammatory cells were situated well below the tumor and separated from it by a broad layer of connective tissue. A large nerve trunk was present below the tumor, but the Bielschowsky method revealed no nerve fibrils in the tumor itself or entering the tumor from the connective tissue below. This may have been due to the condition of the material and to the masses of pigment cells obscuring the field.

This tumor is probably the homologue of the pigmented mole in man, as is suggested by its structure and its position beneath the epithelium. The theories of origin of pigmented nevi are given in substantiation of this relationship.

The epithelial origin was first supported by Unna, who traced a progressive transformation of prickle cells of the epithelium into nevus cells. This theory has been proved by Dawson.

The chromatophore theory and the mesoblastic theory originated with Ribbert, who derived pigmented moles from mesoblastic chromatophore cells. Action, a recent exponent of this view, maintained that in colored races the cells of the basal layer appear pigmented only because of delicate pigmented processes belonging to the melanoblasts, which arborize around the columnar cells and bodies of which lie in the dermis. This theory is not accepted by the majority of workers, who think the pigment granules lie in the protoplasm of the cells of the basal layer and sometimes in the adjoining layer, as well as in the cells of Langerhans. The epidermal Langerhans cells are true melanoblasts and pass pigment to the other cells. Recent work has shown that chromatophores do not originate in the epiblast.

The neural theory was first suggested by Soldan; he found myelinated nerve fibers at the base of the tumor and running into it. He thought nevi were a form of neurofibroma. Masson thought nevi were derived from cutaneous nerve elements. He said the deeper part of the tumor consisted of a plexus derived from nerve fibers which are surrounded by a syncytium with numerous nuclei derived from the cells of the sheath of Schwann or from the supporting cells of the Wagner-Meissner corpuscles. The superficial portion arises from the cells of Langerhans and their homologues, the tactile cells of Merkel-Ranvier. Masson thought that the branched Langerhans cells are connected with cutaneous nerve endings, and that in the deeper structures nerve elements analogous to the tactile

corpuscles of Meissner are found. He accounted for the growth of nevi on the hypothesis that, owing to some malformation, the cutaneous nerve fiber is unable to reach its destination and so forms a plexiform neuroma, while the peripheral elements form a glioma. He pictures the early stages of nevus formation in which the epithelioid nevus cells arise from the cells of Langerhans in the epidermis.

The melanotic tumor found in *Lophius piscatorius* is probably the homologue of the pigmented mole in man. The chromatophore cells of cold-blooded animals are probably homologues of the Langerhans cells, which are the pigment producers of human epithelium. Proof of this and further study of Langerhans cells and chromatophore cells are needed. In fish, a close connection obtains between the chromatophore cells and the nervous system. In *Amphibia*, no such connection has yet been discovered. Masson believed such a connection to exist in warts. The origin of nevi and chromatophore tumors, whether from epithelial or from neural tissue, is still undecided, but is probably the same for both.

#### CHRONIC LIGNEOUS THYROIDITIS (NONSPECIFIC GRANULOMA OF THE THYROID). L. A. MARKLEY.

Chronic ligneous thyroiditis was first described by Riedel in 1896. Since that time about forty-five cases have been reported in the literature.

The clinical features may be summarized as follows: The condition occurs chiefly in persons over 40 years of age. The symptoms are those of constriction and pressure on the esophagus, trachea and recurrent laryngeal nerves. Dyspnea is the most common late symptom. There are no toxic symptoms and no myxedema. The goiter may grow slowly or may increase suddenly. The signs are those of well marked goiter, symmetrical or unilateral. The regional lymph nodes are not enlarged; the overlying skin is not adherent. The most marked feature is the extreme hardness. The surface may be smooth or nodular. The basal metabolic rate is normal.

The present case is shown because of: (1) the difficulty in diagnosis; (2) the possibility of confusion with lymphoid tumor, carcinoma and Hodgkins' granuloma, and (3) the marked feature of atrophy of the glandular tissue of the thyroid.

*Report of Case.*—A white man, aged 65, complained of swelling in the thyroid region of the neck and dyspnea. He had hypertension, fibrillation and arteriosclerosis. The symptoms and signs were characteristic of the condition described. Total thyroidectomy was done. The Wassermann reaction was negative.

The weight of the thyroid gland was 350 Gm. The external surface was finely lobulated and yellowish white. The gland was uniformly hard. The cut surface showed distinct small lobulations; the trabeculae were not visibly emphasized; the color was yellowish white, with several small yellowish cystic areas.

The outstanding microscopic feature was the intense lymphoid infiltration, with follicle formation and germinal centers. There were small areas of eosinophilic infiltration. Among the lymphoid cells were small areas of intact acini, varying greatly in size. These were filled with colloid. The majority of the acini had lost the granular appearance; many under low power appeared like giant cells because of the desquamation and fusion of the acinar epithelium; others had the appearance of proliferating epithelial cells in roughly glandular structure. The lumina of some of the acini contained desquamated epithelial cells and lymphocytes. There were thick strands of fibrous tissue, from which extended finer strands, enclosing degenerating acini and lymphocytes.

In conclusion, the features characteristic of Riedel's struma were noted: (1) extreme lymphoid infiltration, with follicle formation; (2) glandular acini in all stages of degeneration, false giant cell formation, diminution in colloid content, cellular infiltration of the lumina of the acini; (3) increase in the amount of connective tissue, fibrosis and hyalinization; final stage of scar formation, with small foci of lymphocytes and an occasional acinus.



## THYROID GLAND AND GROWTH. FREDERICK S. HAMMETT.

The growth reactions of the body and organs to thyroid deficiency were reviewed in the light of the factors contributive to alterations in the level of thyroid activity. The possible relation of these to long time, unidirectional shifts in environment from the evolutionary point of view was discussed. The paper as a whole was published in the *Quarterly Review of Biology* for September, 1929.

## THE INFLUENCE OF SPLENECTOMY ON THE LEUKOPENIA INDUCED BY THE INJECTION OF CERTAIN FOREIGN SUBSTANCES. ISOLDE T. ZECKWER.

Doan, Zerfas, Warren, and Ames (*J. Exper. Med.* 47:403, 1928) recently reported interesting experiments in which they found that sodium nucleinate injected intravenously into rabbits resulted in marked leukopenia in the peripheral blood, which lasted for a number of hours and which then was succeeded by leukocytosis. They believed that during the peripheral leukopenia, the leukocytes collected exclusively in the spleen, as indicated by leukocyte counts made on the blood from the viscera, and by their finding that after splenectomy, sodium nucleinate resulted in no period of leukopenia, and that leukocytosis then began within a period of time from one half to one sixth of that required in animals in which the spleen was intact.

It seemed of interest to determine whether these observations of the effect of splenectomy applied to the reaction to foreign substances in general or only to the reaction to the specific substance sodium nucleinate. If the spleen should have such a function as storing and then discharging leukocytes, it would be of as great significance as the mobilization of red cells by the spleen from its reservoir, in conditions of great need, as demonstrated by Barcroft.

To determine this point, *Bacillus coli* vaccine was injected intravenously into rabbits, and leukocyte counts were made on the ear blood at frequent intervals after injection. The leukocytes fell abruptly and remained at a low level for several hours. The curves thus obtained were compared with curves obtained after injection of vaccine into the same animals at different times after splenectomy. It was found that splenectomy had no effect on the degree of leukopenia, or on the time of the rise of leukocytes after the leukopenic period.

These results necessitated a reinvestigation of the effects of splenectomy on the leukocyte changes following the injection of sodium nucleinate. Doan and his associates used sodium nucleinate in doses of 1 Gm. per rabbit. When this dosage was used in the present experiments, the animals showed marked circulatory depression. It was found that a much smaller dose, 0.1 Gm. was just as effective in producing leukopenia, and resulted in no obvious vascular changes, so that the animals could be bled readily, and this dosage was well tolerated, so that injections could be repeated frequently for comparison. It was found that in every animal used, splenectomy did not prevent the occurrence of a leukopenia following injection of 0.1, 0.5 and 1 Gm. The time of the rise in leukocytes varied greatly on different occasions in the same animal before splenectomy, and there was no evidence that splenectomy resulted in a more rapid return rise of the leukocytes than the same animals had shown before splenectomy.

With a dose of 1 Gm., the blood pressure fell to a low level on injection of sodium nucleinate, and this low level was maintained for a long time. With a dose of 0.1 Gm., there was a transient fall in blood pressure, but a rapid return to normal, and the leukopenia was maintained, while the blood pressure remained at the normal level.

## HISTOLOGIC GRADING OF TUMORS. STANLEY P. REIMANN.

If a surgeon completely removes a malignant tumor, it will not recur and hence there is no need of grading it. If, on the other hand, fragments are left behind, the chances are overwhelmingly in favor of a recurrence. Since the question in grading tumors seems to be "Will the tumor recur?" it is obvious that the

answer is to be found in the gross aspect and not in the histologic. The most one can possibly do histologically is to estimate the rate of growth of any possible fragments left behind. Since these are present in unknown sizes, numbers and environment, it is impossible in the individual case, to make an accurate prediction. One can only say such and such results were obtained in a large number of cases.

The study of tumor grading includes malignant tumors of the breast, uterus, skin and mucocutaneous junctions. Certain statistical results have been obtained, but they are without value in individual cases except to say that the chances are thus and so. Full details are in preparation.

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*Regular Meeting, May 9, 1929*

HAROLD J. AUSTIN, *President*

CHRONIC LYMPHATIC LEUKEMIA IN A GREEN MONKEY. E. P. CORSON-WHITE.

A case of chronic lymphatic leukemia in a green monkey was presented. This case was discovered at necropsy, when the blood was not in a condition that permitted reliable observation; the diagnosis, therefore, was based on the infiltrative character of the lesions, the absence of distinct tumors and the numerous mononuclear cells in the blood as seen in the sections.

A point of much interest in this animal was the mononuclear exudate at every point of inflammation, notably in the lesions of the jaw, in the erosions of the stomach and in the lesions of the intestines. Similar ulcerations in cases in man, have been reported, especially in the tonsils and the pharyngeal lymphoid tissue and in ulcerated Peyer's patches; these have been described as mononuclear infiltrations at points of inflammation or as purulent destructions of diffuse leukemic infiltrates, but these differ from the observations in the case in question in that the infiltrations occurred where there was normally lymphatic tissue.

The monkey had a great overgrowth of lymphatic tissue, a blood picture characterized by a preponderance of small type, deeply staining basophilic lymphocytes which gave a negative response to the stains for oxydases. The lesions in the separate organs were infiltrative, and there was an absence of any definite tumor formation—a combination that justified a diagnosis of chronic lymphatic leukemia similar to that found in man.

MYCOSIS IN LOWER ANIMALS. FRED D. WEIDMAN.

Owing to the extensiveness of his material, the presenter omitted the section of the paper which dealt with the domestic animals. Mycoses are well known to occur in them, and the frequency of communication to man thoroughly authenticated and described in works on veterinary and human medicine. He confined himself largely to the mycoses that he had observed in the Philadelphia Zoological Gardens; but at the same time, the occurrence in such lowly forms as insects and oysters was included, because as yet they had not been brought together into any one place in medical records. Lesions and micro-organisms were illustrated by lantern slides.

In the Philadelphia Zoological Gardens several cases of ringworm, or dermatomycosis, were met with. In the cases in two young Barbary apes just arrived from the dealer, *Trichophyton gypsum* was established as the cause. Attempts to reproduce the disease in an old horse were unsuccessful; younger subjects were much more liable to this disease, as in man. Ringworm was also encountered in a young chimpanzee. *Trichophyton gypsum* is one of the organisms capable of producing ringworm in man, and there is the obvious possibility of transmission.

Exfoliative dermatitis in the Indian rhinoceros (*Rhinoceros unicornis*) was observed. A yeast species, *Pityrosporum pachydermatis*, was isolated. This organism was closely related to *Pityrosporum ovale*, which is commonly assigned as the cause of seborrhea capitis and other seborrheas of man. The presenter found the same organism in a similar dermatitis of a rhinoceros in the New York Zoological Gardens.

Superficial dermatophytosis in the axilla of a monkey was described. This resembled the seborrheic dermatitis of man, but while the organism was analogous to *Pityrosporum ovale*, there were differences adequate to separate them.

But one other instance of ringworm in wild animals appears to be on record, that of Pinoy, who described a case caused by *Epidermophyton simii*.

Thrush occurred in four Mississippi kites. The condition extended from pharynx to esophagus and stomach. *Oidium* was determined but not the species. Thrush was once encountered in the parrot.

Favus has not been met with in the zoological garden, but reports of its occurrence in wild rats and mice are rather widely scattered through dermatologic literature.

Actinomycosis has been met with in the Philadelphia garden in tapirs, a sable antelope and a cebus. The latter two recovered under potassium iodide therapy.

Kangaroo disease, preeminently of the jaws, and analogous to actinomycosis, was caused by *Nocardia macropodidarum*. It had a greater tendency to generalization than actinomycosis and is a serious problem in the zoological garden.

Nocardiosis was seen in a skunk. This disease is primary usually around the jaws, which frequently become injured during fighting. The infection tends to generalize, producing extensive necroses in the lungs and elsewhere.

Aspergillosis is the most frequently met form of mycosis in the Philadelphia gardens—as many as thirty-four birds dying in a single year. Pigeons, parrots, ducks, eagles and penguins are liable. Flamingoes were concerned in an English zoological garden. *Aspergillus fumigatus* and *Aspergillus glaucus* were the common offenders.

Deep hyphomycosis was observed in sea lions. The writer believed that the organism concerned in this was the largest that has even been described as a pathogen in animals; a single cell as large as 30 microns in diameter and 250 in length. The form, in general, was that of a branching fungus, but the method of reproduction was solely by transverse fission, and the writer felt that it might well be one of the *Algae*. The disease produced was a chronic granuloma with much necrosis and suppuration.

Spontaneous mycosis has been described as occurring in rabbits that were being employed for experiments. This was a report from the literature, and was only cited because it is of importance to laboratory workers.

Among the less spectacular mycoses, but having nevertheless some bearing on the interests of man might be mentioned those of bees due to aspergilli, which effected serious economic losses. Houseflies are liable to a disease produced by *Empusa muscae*, which kills these insects in the autumn. Infections fatal to mosquitoes were produced by *Coelomomyces stegomyiae* and *Zographia notonectae*. *Aspergillus glaucus* and *Aspergillus niger* may be fatal to the larvae of both *Culex* and *Anopheles*. The giant ants of Africa and elsewhere, which are a nuisance to man, were liable to an infection by *Cordyceps myrmecophila*. *Nocardia matricototi* in oysters had occasioned serious economic losses in France.

#### SOME OBSERVATIONS ON THE COMPARATIVE ANATOMY OF THE BREAST. J. W. WAINWRIGHT.

A lantern demonstration was given, showing isolated points in connection with the mammary glands and nursing habits of animals and both savage and civilized women. Among the points illustrated were: the relation of the number of mammary glands and the number of young at birth; the positions of the glands in various animal species with explanations as to why, if only one pair of glands

remained, it should be either in the groin or in the pectoral region; the protected position of the nipples in certain animals, for example the whale and the seal; different racial habits of nursing and holding the baby and instances of women, mostly savage, nursing young animals such as pigs, puppies, etc., out of economic necessity.

SOME OBSERVATIONS ON THE DISTRIBUTION OF PARASITES IN MAMMALS WITH  
THE REPORT OF SOME NEW FORMS. W. P. CANAVAN.

Many well known round-worms having a worldwide distribution and many rare forms were reported. Several changes in systematic position of known forms and confirmation of others were made. Numerous new host-parasite relations and new localities were recorded. Significant cases of parasitism met with yearly were discussed, including the occurrence of superparasitism. No new groupings or combinations were proposed. Emended descriptions of *Trypanoxyuris trypanuris* Vevers (1923) and *Cyrnea colini* Cram (1927) were given. A new name is proposed for *Dirofilaria subcutanea* Linstow (1899), Boulenger (1920) designating it as *Dirofilaria hystrix* nom novum. *Eustrongylides* larvae Ciurea (1924) are included under a new species *Eustrongylides wenrichi*, preadult stages of which were found in a stream pike (*Esox americanus*), nine-spined sunfish (*Enneacanthus gloriosus*), calico bass (*Pomoxis sparoides*), brook trout (*Salvelinus fontinalis*), and a frog (*Rana catesbiana*). New species described are *Acuaria* (*Dispharynx*) *resticula* from the groove-billed ani (*Crotophaga sulcirostris*), *Ascaridia petreusa* from partridge (*Caccabis saxatilis chukar*), *Dirofilaria spinosa* from porcupine (*Erethizon dorsatus*), *Physaloptera multiuteri* from monkey (*Ateles ater*), *Subulura pennula* from quail (*Callipepla squamata*), *Spironoura procera* from terrapin (*Chrysemys rubiventris*) and the aforementioned *E. wenrichi*. The repository of types is the Zoological Laboratory, University of Pennsylvania. In all, there are 162 determinations in 38 genera and 56 species, including new ones, from 150 hosts involving 117 different host species.

## Book Reviews

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HUMAN HELMINTHOLOGY, A MANUAL FOR CLINICIANS, SANITARIANS AND MEDICAL ZOOLOGISTS. By ERNEST CARROLL FAUST, PH.D., Professor of Parasitology in the College of Medicine of Tulane University. Cloth. Price, \$8. Pp. xxii and 616, with 297 illustrations. Philadelphia: Lea & Febiger, 1929.

The human body is subject to attack by a wide variety of parasitic organisms, including bacteria, protozoa, helminths and insects. The different degrees of attention which these groups of parasitic organisms have received from physicians is remarkable, as they have little relation to the importance of the several groups of parasites to the human race. Bacteria have long held the leading place, and are strikingly stressed in all medical schools; it would be difficult to count the number of excellent modern books on bacteriology. The animal parasites, on the other hand, have been more or less neglected, the protozoa somewhat less so than the worms. But among the protozoa are included the etiologic agents of such diseases as malaria, amebic dysentery, kala-azar and trypanosomiasis. The protozoa, however, have little cause for complaint if compared with the parasitic worms or helminths. In most medical schools a small fraction of one semester is devoted to a study of these organisms, and it is doubtful if the average medical man reads one article on helminthology to a hundred on bacteriology and protozoology.

It is natural, in view of the small amount of attention that is paid to the subject in medical schools and the paucity of articles on it in the most widely read journals, that medical men should greatly underestimate the importance of helminthology as a branch of human medicine. It is true that in many localities where modern sanitary conditions prevail helminthic infections have all but disappeared, but the diseases of people in foreign countries are no longer inconsequential to us. The human animal is today travelling farther, faster and oftener, by land, sea and air, than he has ever travelled before. Exotic infections will become established in new places, and imported sporadic infections of foreign origin will occur more and more frequently in places beyond their endemic limits.

It seems, therefore, reasonable to expect that physicians should know at least a little about diseases that affect millions of human beings, even if in a distant part of the world, and have available a source of information about them to which they can refer confidently when more detailed information is desired. In China, 100,000,000 people are yearly exposed to infection with the intestinal fluke, *Fasciolopsis buski*; in Egypt, the vitality of the entire nation is sapped by schistosomes; in western Asia, one fourth of the population of innumerable villages is incapacitated for a month each year by guinea-worms; in every humid tropical and semitropical climate in the world, the vast majority of the inhabitants are infested with hookworms, including a high percentage of the school children in the southern states of the United States; even in parts of the United States there are localities where *Ascaris* and *Trichuris* affect more than half of the children and many of the adults; probably a minority of human beings, even in this country, get through life without affording food and shelter for pinworms (oxyurids). In addition to these there are to be considered the frequent occurrences of various tapeworm infections, trichiniasis, filariasis and a large list of minor infections from worms to which the human body is subject. In the seventeenth century 4 human worm parasites were known; in the early part of the nineteenth century there were 12; in Faust's book are listed 103, of which 30 are common human parasites.

Faust's work is strongly recommended as a reference book. Faust himself not only has taught helminthology to physicians and zoologists for nearly two

decades but has made highly important original contributions to knowledge in every important phase of the subject, and on all the important groups of parasites, and he is therefore qualified, as few others are, to write such a book as he has written. The information contained is thorough and up to date, and contains surprisingly few errors. It is not a mere sterile description of the worm parasites of man, which many books on parasites are; it contains accurate information on life histories, epidemiologic factors, pathology, diagnosis and methods of treatment and prevention. After some introductory chapters on general parasitologic subjects, such as interrelations of parasites and hosts, history, geographic distribution, the basis for scientific names and a discussion of literature, with a list of important books which deal with helminthology and of periodicals which frequently contain important papers on the subject, the author goes on to discuss the various groups of helminthic parasites—flukes, tapeworms and nematodes—first in general, and then in detail, giving the most essential facts of what is known concerning each species. The classification and systematic position of the parasites are carefully considered, but are largely segregated in separate sections, so that this phase of the subject, which is of more interest to zoologists than to physicians, does not encumber the text as much as it otherwise might. In the latter part of the book there are several chapters dealing with methods, which should prove useful. At the end of the several sections are given bibliographies of important papers dealing with the several parasites or groups of parasites, from which the reader can get a clue to the entire literature on the subject. In the matter of nomenclature, which has always caused much trouble in parasitology on account of its instability, Faust is, in the abstracter's opinion, a little ultramodern in a few instances, but there should be little difficulty in finding parasites under the names by which they are better known in medical literature, for synonyms are given and are included in the index.

The book is exceptionally well illustrated, a high percentage of the figures being original, which is unusual in a book of this sort. The arrangement and construction of the book are excellent and it is attractive in appearance. Both the author and the publisher are to be congratulated on a fine and valuable piece of work. It is a book which every physician would do well to include in his library, for, as intimated, it deals with a subject worth knowing something about, and there is no other book which can take its place as a comprehensive, authoritative, up to date treatment of human helminthology. The publication of the book is an occurrence of more than usual interest—it marks an important milepost in the progress of the subject with which it deals. Helminthology has advanced at astonishing speed in the last ten or fifteen years; it has, in fact, advanced faster in that period than any other field of medicine, so far as the reviewer is aware. Its progress since 1915 has been comparable with the years from 1880 to 1900 in bacteriology. It is, therefore, an ideal time for a book to appear which brings this scattered mass of information together, to make easier the paths of those who will in the future carry the subject further.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. Volume 12. Pathology of the Acute Respiratory Diseases and of Gas Gangrene Following War Wounds. Prepared under the direction of Major General M. W. Ireland, Surgeon General. By Major George R. Callender, M.C., and Major James F. Coupal, M.C. Price, \$3.60. Pp. 583. Washington, D. C.: United States Government Printing Office, 1929.

This is essentially an atlas. A little more than one half of the volume is filled with illustrations most of which occupy an entire page. These are supplemented by twenty-five colored full page plates. All the illustrations are from photographs, and in praising them only superlatives are appropriate. Together with some directions for staining microscopic preparations, the methods used in making the photographs are described in an appendix. The account of influenza and other respiratory diseases responsible for so many deaths among

American soldiers in cantonment hospitals here and in troops abroad is almost altogether an amalgamation of articles released during the war by the Surgeon General for publication in medical journals. In footnotes and in fine print, acknowledgment is made for the sources of this material. About thirty-six such articles are mentioned. Following this and scattered among the illustrations are about thirty pages by Major Callender in which the pathologic anatomy is discussed under the following headings: lobar pneumonia, interstitial pneumonia, peribronchial pneumonia, lesions associated with infection by *B. influenzae*, secondary bronchopneumonia, spreading bronchopneumonia (interstitial), acute bronchitis and pneumonitis without consolidation, secondary lobular pneumonia and interstitial lymphangitis with finally another subdivision on staphylococcal pneumonia from the report by Chickering and Park (*J. A. M. A.* 72:617 [March 1] 1919).

This portion of the work is an elaborate legend for the illustrations. Many of the photographs, especially those of gross morbid anatomy, fairly glow with enlightenment. Great credit is due those who labored so faithfully during the war to prepare the museum material drawn on for these photographs. Involvement of the nasal cavity and its accessory sinuses is only casually mentioned. Such material probably was not secured in abundance.

The second section by Major Coupal on gas gangrene following war wounds conforms to reports of scientific studies as they appear in the best medical journals and monographs. There are numerous evidences of a thorough understanding of the subject by the author. For example, allusion is made in the bibliography to studies of gas gangrene and its bacteria carried out in foreign countries and other places outside governmental purview. The atlas feature also prevails in this section, since it has 10 of the colored plates and 144 other illustrations.

Publications from official bureaus and other branches of the government usually have peculiarities of make-up and material which put them in a different class from textbooks or journalistic literature. They are largely storehouses and often a prolonged search is necessary to find desired information. No such difficulty will confront those who consult this volume for visualizable conceptions of the diseases so elaborately portrayed.

**THE ORIGIN OF MALIGNANT TUMORS.** By THEODOR BOVERI, University of Würzburg. Translated from German by Marcella Boveri, with a foreword by Maynard M. Metcalf, Johns Hopkins University. Cloth. Price, \$2.50. Pp. 128. Baltimore: Williams & Wilkins Company, 1929.

This is a translation by Boveri's wife, also a biologist, of the brochure "Zur Entstehung der malignen Tumoren" which was first published in 1914 by Gustav Fischer in Jena. When it appeared Boveri for a number of years had been recognized as one of the foremost authorities on the finer visible phenomena accompanying indirect cell division. By experiments with eggs of sea urchins he had succeeded in producing forms of pathologic karyokinesis corresponding to the multipolar and asymmetric division which occurs in many varieties of malignant tumors. He claimed that such abnormal methods of division of nuclei came about because wrong combinations of chromosomes formed the new nuclei. Application of the results of these studies of low forms of animal life to the genesis of tumors led to this work.

The trend of investigation of the origin of malignant tumors during the decade and a half since 1914 has been definitely away from problems of morphology toward others more closely related to the body as a whole. Modern conceptions of tumors are disposed to account for the anaplasia of von Hanseemann and its corresponding deviations of nuclear division, studied so precisely by Boveri, as expressions of the characteristics possessed by tumor cells and not as causes of their rapid proliferation. The actual causes are being sought in disturbances of physicochemical balance and metabolism, in systemic disease and in familial

dyscrasias. At some future time tumor research perhaps may be directed again to peculiarities of tumor cells and to their unusual ways of multiplying. In any event there is no doubt that the relation these pathologic mitoses bear to those experimentally produced by Boveri will not escape recognition when the ultimate pattern of the etiology of tumor lies plainly before us.

Published as it was at the beginning of the war, but few copies of this work passed out of Germany. Its appearance in English is consequently bound to meet with general approval. Its discussion of chromosome irregularities is masterly and clear; the English rendition is carefully done with considerable evidence of an effort to simplify the somewhat involved and long German sentences. At present the chief value of the work is the charm of the critical thinking exhibited by the author in discussing evidence favoring, and that opposed to, his hypothesis. For younger men beginning a career of technical investigation in medicine, this presentation affords an unusual opportunity to become intimately acquainted with the care exercised by one trained in the ways of science.

A MANUAL OF EXTERNAL PARASITES. By HENRY ELLSWORTH EWING, United States Bureau of Entomology. Price, \$4.50 (by mail, \$4.66). 96 illustrations. Springfield, Ill.: Charles C. Thomas, 1929.

The main object of this book is to furnish brief sketches of the principal morphologic characters of the external parasites, their life histories and their natural relationships. The parasites in question are the mites, the ticks, the biting lice, the sucking lice and the fleas. This includes the rat flea concerned in the transmission of plague; the itch mite; the ticks of Rocky Mountain spotted fever, of Texas fever, and of spirochetosis of fowls; the sucking lice of relapsing fever, of trench fever and of typhus fever. In preparing the keys for identification, the large collection of parasites recently given to the National Museum by Dr. E. A. Chapin was found of great help. This collection is in the charge of the author. There is an abundance of good black and white illustrations, and the book contains a large amount of detailed and exact information clearly set forth, with valuable suggestions for control and protection.



## Books Received

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THE AUTONOMIC NERVOUS SYSTEM. By Albert Kuntz, Ph.D., M.D., Professor of Anatomy, St. Louis University School of Medicine. Cloth. Price, \$7 net. Pp. 576, with 70 illustrations. Philadelphia: Lea & Febiger, 1929.

THE PATHOLOGY (PATHOLOGIC ANATOMY) OF THE EYE. By Jonas S. Friedenwald, A.M., M.D., F.A.C.S., Associate in Pathological Ophthalmology at the Johns Hopkins University; Pathologist of the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. Illustrated with 253 figures, mainly photomicrographs from the Pathological Collections of the Wilmer Ophthalmological Institute and the Army Medical Museum, by Helenor Campbell. Price, \$4.50. Pp. 346. New York: The Macmillan Company, 1929.

DIAGNOSTIC VALUE OF THE "VACCINIA VARIOLA" FLOCCULATION TEST. By W. L. Burgess, James Craigie, and W. J. Tulloch. Medical Research Council, Special Report Series, 143. Pp. 43. Price, 1 shilling 3 pence, net. London: His Majesty's Stationery Office, 1929.

THE DEVELOPMENT AND GROWTH OF THE EXTERNAL DIMENSIONS OF THE HUMAN BODY IN THE FETAL PERIOD. By Richard E. Scammon, Professor of Anatomy, University of Minnesota, and Leroy A. Calkins, Professor of Obstetrics and Gynecology, University of Kansas. Price, \$10. Pp. 365, with 73 illustrations. Minneapolis: The University of Minnesota Press, 1929.

MOLECULAR PHYSICS IN RELATION TO BIOLOGY. By M. Ascoli, Robert Chambers, A. de Coulon, F. G. Donnan, N. E. Dorsey, Leonor Michaelis, John H. Northrop, P. Lecomte du Noüy, W. J. V. Osterhout, William Seifriz and F. Vlés. Bulletin of the National Research Council, 69. Price, \$3. Pp. 293. Washington, D. C.: National Research Council, 1929.

BLOOD GROUPING IN RELATION TO CLINICAL AND LEGAL MEDICINE. By Laurence H. Snyder, D.Sc., Associate Professor of Zoology, North Carolina State College, Raleigh; Committee on Blood Grouping, National Research Council. Price, \$5. Pp. 153 with 28 illustrations and 5 plates. Baltimore: Williams & Wilkins Company, 1929.

HOOKWORM DISEASE: ITS DISTRIBUTION, BIOLOGY, EPIDEMIOLOGY, PATHOLOGY, DIAGNOSIS, TREATMENT AND CONTROL. By Asa C. Chandler, M.Sc., Ph.D., Professor of Biology, Rice Institute, Houston, Texas; recently Officer-in-Charge, Hookworm Research Laboratory, School of Tropical Medicine and Hygiene, Calcutta, India. Price, \$5. Pp. 494, with 33 illustrations. New York: The Macmillan Company, 1929.

EDEMA AND ITS TREATMENT. By Herman Elwyn, M.D., Assistant Visiting Physician, Gouverneur Hospital, New York. Price, \$2.50. Pp. 182. New York: The Macmillan Company, 1929.

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